Working memory in depression: a functional magnetic resonance imaging study

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I declare that this thesis embodies the results of my own work and that I alone have composed it. No sections of this thesis have appeared in print anywhere else, and none of the data from the key experimental investigations that comprised this study have previously been submitted for any other degree or professional qualification. In accordance with normal academic conventions I have made due acknowledgement to the work of others.

Signed:

Date: 27th April 2004

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Abstract

The impact upon cognitive function as a result of major depressive disorder (MDD) has been consistently documented, with depressed individuals demonstrating extensive and varied cognitive deficits. The pattern of deficits seen in MDD could be partially explained by a dysfunction of working memory. However, attempts to determine whether or not depressed individuals are in fact impaired on tasks reliant on working memory have produced results that are inconsistent. Yet, both resting state and activation studies of patients with MDD have identified functional impairments in regions of cortex commonly associated with normal working memory function in healthy adults. The main aims of this series of investigations were to determine (1) whether individuals with a diagnosis of major depression where significantly impaired on a parametric working memory task (i.e. the n-back task), compared to matched controls, and (2) whether any significant difference between the experimental groups was associated with a significant group difference in cortical activation during performance of the task (i.e. using BOLD fMRI). It was determined that the consumption of anti-depressant medication in the patient group was a potential confounder of any observations in the first two experiments. Thus, additional aims of this study were to determine (3) whether the administration of anti-depressant medication had any significant behavioural effect upon performance on the n-back task, and (4) whether the consumption of anti-depressant medication had any significant effect upon the pattern of activation observed during performance of the task. In order to address these aims three experimental studies were conducted. (1) Experiment One: Working Memory in Depression: The performance of twenty individuals with MDD and twenty matched, healthy controls was assessed on the n-back task (i.e. accuracy (percentage correct) and reaction time (msec)). Analysis of the data revealed a significant main effect of participant group with regards to both accuracy and reaction time (i.e. $F_{(1, 38)}=5.93$, $p = 0.02$ *and* $F_{(1,38)}=25.16$, $p < 0.001$, *respectively), with patients showing lower mean accuracy scores, and higher mean reaction times. (2) Experiment Two: Working Memory in Depression: a functional MRI study: Ten individuals with MDD and ten matched, healthy controls undertook the n-back task while undergoing fMRI scanning. Analysis of the behavioural data revealed a significant main effect of participant group on mean accuracy scores (i.e.* $F_{(1,18)}= 4.727$, $p = 0.043$*), with patients exhibiting lower average scores across all task levels. However, there was no significant main effect of participant group on mean reaction time. Analysis of the functional imaging data, using SPM99, revealed a significant difference between patients and controls in the level of activation in the medial orbital prefrontal cortex/ subgenual anterior cingulate with increased task difficulty, i.e. level of activation in patients was greater in this region compared to controls (i.e.* $K_E=128$, $p_{(corrected)}=0.025$*). (3) Experiment Three: The effect of escitalopram on working memory in normal, healthy adults: A functional MRI study: Ten healthy volunteers were given escitalopram for 7 consecutive days, i.e. 10mg/day. Participants were scanned while medication free and on the final day of their prescription. The consumption of escitalopram did increase participants' subjective assessment of state anxiety (i.e.* $t_{(9)} = -2.172$, $p = 0.029$*), but there was no effect of medication status on either aspect of behavioural performance on the n-back task. Random effects analysis of the functional imaging data revealed no significant differences between conditions with regards to the level of activation in any area of cortex. Overall, the results of this study were indicative of a significant dysfunction of working memory in individuals with major depression. Furthermore, it would appear that this observed dysfunction was associated with a quantitative difference in the level of functional activation in the medial orbital prefrontal cortex/subgenual anterior cingulate in depressed patients. Moreover, the results of the final experiment in this series allow us to speculate that the differences, both behavioural and functional, noted between patients and controls are the result of an underlying factor in the aetiology of depressive illness rather than an effect of anti-depressant medication.*

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Abbreviations and acronyms

^{18}FDG	^{18}F-fluorodeoxyglucose
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxy-tryptamine (serotonin)
^{99m}Tc	technetium-99m
AC	anterior cingulate
ACT	Auditory Consonant Trigrams Test
AD	Antidepressant
APSAQ	Alderley Park State Anxiety Questionnaire
APT	Automated Psychological Test
AVLT	Auditory Verbal Learning Test
BA	Brodmann area
BD	bipolar depression
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory – II
BNT	Boston Naming Test
BOLD	blood oxygen level dependent (fMRI)
BPRS	Brief Psychiatric Rating Scale
CAMDEX	The Cambridge Examination for Mental Disorders of the Elderly
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAS	Clinical Anxiety Scale
CID	Clinical Interview for Depression
COWAT	Controlled Oral Word Association Test
CPT	Context Processing Test
CVLT	California Verbal Learning Test
CVMT	Continuous Visual Memory Test
DA	Dopamine
DART	Danish Adult Reading Test
DAT	Alzheimer-type dementia
DGB	Digit Span Backward
DGF	Digit Span Forwards
DHEA	Dehydroepiandrosterone
DLPFC	dorsolateral prefrontal cortex
DMTS	delayed match-to-sample
DOPA	dihydroxyphenylalanine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition
DSST	Digit Symbol Substitution Test
ECD	Elevator Counting with Distraction (subtest of the TEA)
ECT	electroconvulsive therapy
EEG	electroencephalography
ELFT	Exclude Letter Fluency Test
EMG	electromyogram
EP	evoked potential
EPI	echo planar imaging
ERP	event related potential
fMRI	functional magnetic resonance imaging
FPDD	familial pure depressive disorder
GBS	Gottfries-Brane-Steen dementia rating scale
GDS	Global Deterioration Scale
HC	Hippocampus
HRSD	Hamilton Rating Scale for Primary Depressive Illness

ICD-10	International Statistical Classification of Diseases and Related Health Problems – Tenth Revision
ISI	inter-stimulus interval
KAIT	Kaufman Adolescent and Adult Intelligence Test
LNNB	Luria-Nebraska Neuropsychological Battery
LORETA	low-resolution electromagnetic tomography
LTM	long-term memory
MADRS	Montgomery- Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MCST	Modified Card Sorting Test
MDD	major depressive disorder
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Exam
MOPFC	medial orbital prefrontal cortex
MPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NA	Noradrenaline
NART	National Adult Reading Test
OCD	obsessive compulsive disorder
OFC	orbito-frontal cortex
PASAT	Paced Auditory Serial Addition Test
PET	positron emission tomography
PFC	prefrontal cortex
RAVLT	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
RCBF	regional cerebral blood flow
rCMRglu	regional cerebral glucose metabolism
RFFT	Ruff Figural Fluency Test
RMT	Warrington Recognition Memory Test
rAC	rostral anterior cingulate
ROCF	Rey-Osterrieth Complex Figure Test
SAC	Stress Arousal Checklist
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-IV
SMTS	Simultaneous Match-to-Sample
SPECT	single photon emission computed tomography
SSRI	selective serotonin reuptake inhibitor
STM	short-term memory
TCA	tricyclic antidepressant
TEA	Test of Everyday Attention
TOL	Tower of London (test)
VE	Visual Elevator (subtest of the TEA)
VLPC	ventrolateral prefrontal cortex
WAIS-R	Weschler Adult Intelligence Scale –Revised edition
WCST	Wisconsin Card Sorting Test
WM	working memory
WMS-R	Weschler Memory Scale – Revised edition
WRAT-R	Wide Range Achievement Test – Revised edition

Chapter 1: Literature Review

1.1 Major Depression

1.1.1 Epidemiology of major depression

Major depressive disorder (MDD) is a psychiatric illness that is not only common in the general population but is of significant personal and social concern. Individuals suffering from depression commonly experience reduced productivity and quality of life, in conjunction with a significant increase in mortality (Doris, Ebmeier & Shajahan, 1999). Moreover, the World Health Organisation's Global Burden of Disease project rated depressive illness as the second major cause of disease burden in developed countries, and has predicted this burden to increase (Patten, 2003).

Understanding the impact of major depression is reliant on access to accurate epidemiological data. However, as a result of varied methodological approaches accurate epidemiological data is difficult to obtain. These methodological differences extend not only to the operational definitions of depression employed in individual studies but also to sampling methods and methods of data acquisition. While some studies have examined the incidence and prevalence of major depression via community studies (e.g. Kessler et al., 2003), other epidemiological investigations have relied on the clinical records of individuals receiving treatment for affective disorders in a given region. However, despite the differences in methodology between studies it is possible to obtain a reasonable impression of the general epidemiology of major depression by considering the comparative evidence from studies that have employed different methodological approaches.

One indication of the incidence of depression in the general population is the number of individuals currently receiving either in- or outpatient hospital care for affective disorders. In 2001-2002 there were 52,569 hospital admissions for affective disorders in England and Wales (source: Department of Health, United Kingdom, http://www.doh.gov.uk, accessed 28/10/03). In this same period it was estimated that worldwide cases of unipolar depression amounted to 150,762,000 out of an estimated total population of 6,122,210,000 (i.e. approximately 2.5%; source: World Health Organisation, Global Burden of Disease Study, http://www3.who.int, accessed 28/10/03).

However, community based surveys have estimated that the true incidence may be greater than consideration of hospital admissions may indicate. The advantage of this type of approach is that it allows for the inclusion of individuals who may be experiencing symptoms of depression but who do not seek treatment to be in incidence estimates. A recent community based survey of a sample of 9090 American adults predicted the lifetime rate of MDD to be around 16%, with a 12-month rate of 6.6%.

Epidemiological studies of the rate of depression also indicate an increase in the incidence of unipolar affective disorders, in conjunction a successive decrease in the average age of depressed cohorts across time. Although it may be argued that these changes are the result of social or environmental influences on the rate of depression, it is imperative to consider alternative explanations for the apparent alterations in the characteristics of depressed individuals. Indeed, there are a variety of potential explanations for these changes in the demographics of the MDD population. For example, the increased incidence of unipolar depression may reflect changes in diagnostic criteria or increased likelihood of presentation, as opposed to a genuine change in the prevalence of major depression. Similarly, the successive decrease in the mean age of depressed populations may be attributed to a greater awareness of the likelihood of affective disorders in adolescent populations that may influence the probability of diagnosing major depression in younger individuals, rather than the presence of affective disorders in younger cohorts being a novel phenomenon.

1.1.2 Defining major depression

'Depression' commonly denotes a general lowering of mood, or feeling of sadness. Yet, the experience of the clinically depressed individual could reasonably be defined as being more severe than this commonly accepted definition infers. It is, therefore, imperative to establish the boundary between the normal experience of sadness and the pathological state that constitutes depressive illness. However, in order to make this distinction it is essential to appreciate the complexity of the range of symptoms that characterise major depression. Indeed, clinically depressed individuals will not only experience a lowering in their mood, but may also endure a loss of interest in or ability to experience pleasure and feelings of worthlessness and guilt. Moreover, individuals with major depression will also commonly exhibit changes in thought, activity, social behaviour, and vegetative functions (Beaumont, Kenealy & Rogers, 1999).

The diagnostic criterion for a major depressive episode (MDE) in DSM-IV (American Psychiatric Association, 1994) reflects the intricacy in depressive symptomology. The DSM model of MDE is inclusive of alterations of mood, pleasure, and body weight, disorders of sleep, psychomotor retardation or agitation, feelings worthlessness or guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicidal ideation. Within this framework major depressive disorder (MDD) is defined as the occurrence of one or more major depressive episodes.

Despite certain commonalities in the experience of major depression, the pattern of symptoms observed in depressed patients can vary quite dramatically between individuals. This also needs to be accounted for in any reasonable attempt at classification. Therefore, rather than adopting a monothetic approach to defining depression – i.e. where all properties are both necessary and sufficient for classification – diagnostic tools such as DSM-IV assume a polythetic approach. Within this approach an individual may be diagnosed as suffering from depression if they exhibit a selection of the properties that have been defined as characteristic of this particular class of illness. Moreover, this approach recognises that a significant proportion of patients may experience a specific symptom (or symptoms) but that no single symptom is necessary or sufficient for diagnosis.

The complexity of depression is evident in approaches to classifying depressive illness is also reflected in measures of severity of depressive illness. There are numerous indices available for determining the intensity of an individual's depression, for example measures such as the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Hamilton Rating Scale for Primary Depressive Illness (HRSD) (Hamilton, 1967). Both of these measures consider the potential spectrum of depressive symptoms in their assessment of severity of depression.

Therefore, in empirical investigations of major depression it may be more productive to consider an operational definition of major depression that relies on clinical diagnosis in conjunction with an appropriate measure of symptom severity. The outcome of this approach is an operational definition of unipolar, major depressive illness that allows us to appreciate the complexity of the experience of depressive illness. Moreover, this approach to the classification of depressed participants in experimental studies can enable the

determination of the relative impact of different aspects of depression and its severity on other experimental measures.

1.1.3 Profile of cognitive function in major depression

Major depression is not only defined by the presence of certain abnormalities in affect, but is also characterised by dysfunction in aspects of cognitive function. While unipolar depression is commonly associated with the disorder of psychological constructs such as attitudes or attributions, individuals with depression also exhibit a tendency to experience dysfunction in the more general processing, storage, and retrieval of information. It is this latter dysfunction of cognition that is the focus of this section.

Neisser, (1967) defined cognition as "all the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used" (p.4). Thus, within this framework the term 'cognition' may be defined as those functions pertaining to sensation, perception, imagery, attention, recall, memory, problem solving, and thinking. Consequently, cognitive dysfunction may be defined as a disorder of any or all of these processes.

In order to ascertain the cognitive profile in unipolar depression there are a number of factors that it is necessary to consider. Firstly, cognitive dysfunction has traditionally been considered a transitory aspect of depressive illness and may only last as long as the depressive episode (Bazin et al., 1994; Moffoot et al., 1994; Elliott, 1998). However, recent evidence has been indicative of persistent deficits in cognition in chronic and treatment resistant cases of depressive illness (Kessing, 1998). The persistence of cognitive deficits may be associated with depressive subtype (Austin et al., 1999) or treatment, e.g. electroconvulsive therapy (ECT). In addition, as with the expression of other symptoms, cognitive dysfunction observed during a MDE can vary between individuals in both nature and severity.

Therefore, in order to determine a model of cognitive dysfunction in major depression it is imperative to consider: (1) whether there is reasonable evidence of cognitive dysfunction in major depression; (2) the profile of cognitive deficits commonly observed in major

depression; (3) the factors that underlie such dysfunctions; and (4) whether such deficits are trait or state aspects of depressive illness.

1.1.3.1 Summary of cognitive deficits in major depression

A considerable volume of research literature has been concerned with cognitive function associated with depressive illness. However, there have been notable differences in the outcomes of such investigations. While some studies have noted a significant deficit in depressed patients in a number of different cognitive processes (e.g. Austin et al., 1992; Brown et al., 1994; Moffoot et al., 1994; Beats, Sahakian & Levy, 1996; Elliott et al., 1996; Austin et al., 1999; Landro, Stiles & Sletvold, 2001; Ravnkilde et al., 2002), others have found no or little evidence of impairment in measures of cognitive function (e.g. Miller et al., 1991). This variability in empirical observations between studies makes it difficult to ascertain whether there are reasonable grounds for presuming a pattern of specific cognitive impairment in major depression, or whether depressed individuals experience a global impairment of cognitive function.

One possible explanation is that the inconsistencies in experimental findings between different studies have arisen from the substantial diversity in approaches to studying cognitive function in major depression. While some studies have been relatively conservative in their choice and definition of depressed samples, examining deficits in clearly defined sub-samples of depressed individuals, others have considered cognitive function in more diverse samples of patients, e.g. including individuals with unipolar and bipolar depression (BD), and with various between subjects differences in history and symptom presentation. Similarly, studies have also been relatively diverse in the cognitive processes that they studied and the assessments employed, e.g. while some studies have examined a variety of aspects of cognition using well known neuropsychological batteries, others have chosen to examine single cognitive functions with less well known or specially designed tasks.

The methodological variation between studies makes it a potentially complex task to ascertain a reliable model of the cognitive function in individuals with MDD. A potential solution to this issue is to determine those cognitive functions that are consistently noted as being impaired in depressed patients across studies and that appear to show a deficit

associated with the affective facets of depressive illness. This may be achieved by ascertaining commonalities in the approaches of different investigators, and by identifying similar observations between studies, irrespective of the similarities or differences in experimental methodologies.

Bearing this in mind, the aim of this section is to review the literature pertinent to cognitive function in depression in order to ascertain the potential profile of cognitive deficit in major depression. Although important relationships do exist between a number of the cognitive functions explored here, some processes which are intrinsically linked (e.g. information processing and attention) have been dealt with separately.

(Note: A summary of the original articles and review papers examining cognitive and neuropsychological deficits in depression which were considered in this review are presented in Appendices 1A and 1B).

Psychomotor function

Disturbance of psychomotor function is a common aspect of unipolar depression. Psychomotor dysfunction is so commonplace in patients suffering from MDD that it is included as a diagnostic criterion in classification systems such as DSM-IV and ICD-10. One potential reason for its inclusion may be the high predictive value of psychomotor dysfunction for the presence of depressive illness. Indeed, in an examination of the predictive value of each individual diagnostic criteria on DSM-III one study found that psychomotor change was one of the best predictors of MDD (i.e. Buchwald & Rudickdavis, 1993).

The profile of psychomotor function observed in depressed patients includes both psychomotor retardation and agitation. Moreover, impairment has been noted in varied aspects of psychomotor function such as gross motor activity, body movement, speech, and motor response time (Sobin & Sackeim, 1997). Despite the importance of all of these factors in accounting for psychomotor disturbance in major depression, in this instance our concern is with those aspects pertaining to cognitive function.

A number of investigations have observed psychomotor dysfunction associated with the performance of tests of cognition (e.g. Beats et al., 1996; Austin et al., 1999, Moffoot et al., 1994; Ilsley, Moffoot & O'Carroll, 1995; Moritz et al., 2002; Ravnkilde et al., 2002). These studies have all noted evidence of psychomotor slowing in individuals with major depressive illness compared to matched, healthy controls, on a number of different cognitive measures. The assessments used in these investigations have included both simple and choice reaction time (RT) tasks (i.e. Beats et al., 1996; Austin et al., 1999), measures of verbal fluency (i.e. Beats et al., 1996; Austin et al., 1999), the digit symbol substitution (DSST) of the Wechsler Adult Intelligence Scale – Revised (WAIS-R: Wechsler, 1981; i.e. Moffoot et al., 1994; Ilsley et al., 1995; Ravnkilde et al., 2002), the reaction time measure of the Cambridge Automated Neuropsychological Test Battery (CANTAB: Robbins et al., 1994; i.e. Moffoot et al., 1994), and the Trails A and B tasks (Reitan, 1992; i.e. Moritz et al., 2002; Ravnkilde et al., 2003).

However, not all studies that have considered psychomotor function in MDD have found evidence of significant deficits. In a study of one hundred and twenty three depressed outpatients, Grant and colleagues found no evidence of psychomotor dysfunction in depressed patients compared to controls on the Trails A task (Grant, Thase & Sweeney, 2001). Likewise, the failure to observe any significant deficit in psychomotor function has also been noted in other investigations, on a range of neuropsychological measures (e.g. Miller et al., 1991; Sweeney, Kmiec & Kupfer, 2000).

Despite the contradictory indications of these latter findings there does appear to be greater support for the notion of psychomotor slowing in major depression. For example, in a review of cognitive function in MDD, which considered papers over a period of twenty-two years, Veiel concluded that there was evidence of psychomotor slowing across studies (Veiel, 1997). A number of studies that met the inclusion criteria for the review found that on choice reaction time measures patients with MDD performed worse than controls. Moreover, one of the studies included in this review had considered both electrophysiological and behavioural measures of psychomotor performance. The authors proposed that the deficit seen in choice reaction time in depression was not due to the slowing of perceptual processes, but rather could be attributed to slowing of the response processing stages (i.e. Knott & Lapierre, 1987).

Consequently, it is reasonable to conclude that there is evidence of psychomotor slowing associated with performance of cognitive tasks in patients with major depression. However, while these studies provide rather consistent evidence of psychomotor impairment in major depression, there are number of important factors regarding these studies that should be noted. Firstly, Austin and colleagues noted that while there was clear evidence of psychomotor retardation in a sub-group of melancholic patients compared to healthy controls, non-melancholic patients were largely unimpaired (Austin et al., 1999). In addition, Moffoot found that in depressed patients with a diagnosis of melancholia and clear diurnal variation in mood, the degree of psychomotor deficit seen in patients was more severe and extensive in the morning (Moffoot et al., 1994).

It is also important to note that this particular deficit does not appear to be task specific. The generalised nature of psychomotor dysfunction in depressed patients has been suggested as evidence for the notion that psychomotor retardation may be a causal factor in the range of cognitive dysfunctions observed in MDD. Nonetheless, studies that have observed psychomotor dysfunction in samples of depressed individuals have observed that when psychomotor performance is included as a co-variate in analysing cognitive performance that it cannot account for the difference seen between patients and controls on all measures of cognitive performance (i.e. Ravnkilde et al., 2002). Moreover, studies that have failed to find differences between MDD patients and healthy controls on measures of psychomotor function have still observed depression associated deficits on other measures of cognitive function, such as performance on the Wisconsin Card Sorting Test (WCST; Heaton, 1981) (i.e. Grant et al., 2001), attention (i.e. Miller et al., 1991), and episodic memory (i.e. Sweeney et al., 2000).

Information processing

- Effortful vs. automatic processing

It has long been a popular notion that the resources available to an individual for cognitive processing are limited. Moreover, it has been suggested that the amount of processing required varies between different tasks (Kahneman, 1973). This further implies that different tasks place unequal demands upon the information processing system, resulting in different classes of information processing tasks.

Broadly speaking one can separate the types of information processing that individuals require to perform cognitive tasks into 'effortful' and 'automatic' processes (Hasher & Zacks, 1979). 'Effortful' tasks are defined as those cognitive tasks that an individual must initiate intentionally, which are amenable to the effects of practice, and which place a high level of demand upon the attentional resources of the information processing system. In addition, effortful tasks also show a tendency to interfere with the ability of an individual to effectively process other tasks that also require attentional resources. 'Automatic' tasks, on the other hand, occur without conscious awareness and intention, do not benefit from practice, and place minimal demand upon attentional resources. Moreover, a task that is automatic in nature should not interfere with the processing of cognitively demanding tasks (Posner & Snyder, 1975).

Although the distinction between effortful and automatic information processing is one that is useful both theoretically and in research settings, cognitive theorists have suggested that it is not sufficient to describe all cognitive processes in terms of just these two categories, and that instead information may be better described in terms of a continuum of automaticity.

Major depression is commonly associated with increased levels of state stress, which may be contributory to the profile of information processing function observed in MDD. Hasher and Zacks (1979) argued that conditions of stress place demands upon attentional resources, and as a result would be expected to interfere with the effective processing of effortful cognitive tasks, but not automatics ones. Consequently, it has been postulated that MDD will be associated with an impairment of tasks that place high demands on attentional resources, i.e. effortful tasks, and a relative sparing of low demand, i.e. automatic, tasks, as a result of stress-mediated demands on processing resources (e.g. Hartlage et al., 1993). This notion has been supported by evidence from a number of investigations which have noted a significant difference between depressed patients and healthy controls on measures of effortful processing (e.g. Golinkoff & Sweeney, 1989; Roy-Byrne et al., 1986; Beats et al., 1996; Thomas, Goudemand & Rousseaux, 1999).

One of the most extensive reviews of automatic and effortful processing was conducted by Hartlage and colleagues (i.e. Hartlage et al., 1993). This review considered a wide range of mnemonic and non-mnemonic cognitive tasks, including: intellectual functioning; problem

solving; general learning; encoding; reading; psychomotor retardation; and automatic processing (e.g. frequency encoding, spatial location, and activation of self-relevant content). The authors concluded that depression was associated with an impairment of effortful processing, across a range of tasks. Conversely, it was observed that depressed individuals experienced only a minimal amount of interference in automatic processing. They further noted that the level of impairment was related to the degree of effortfulness of the task, severity of depression, and the valence of the stimulus material used.

Despite the obvious discrepancies in the performance of effortful and automatic tasks noted in depressed individuals there remains the issue of whether this difference is due to the degree of automaticity or effortfulness required by the task or whether it can be attributed to some other factor of performance. It has been suggested that the difference between the two types of task may simply be the result of differences in the degree of difficulty of tasks. By their nature effortful tasks do tend to be more complex and difficult to perform, while automatic tasks are often more simple and easier to perform. Thus, it is essential that this difference be taken into account when considering the evidence of impairment in information processing associated with major depression.

Irrespective of how the available data is interpreted, there is considerable evidence of impairment in effortful information processing associated with depression. However, at least one paper concerned with relative performance of patients and controls on measures of automatic and effortful tasks noted that the difference in performance between tasks could not be solely explained by the level of automaticity (i.e. Thomas et al., 1999). In this study individuals with major depression were compared to healthy controls on levels of a task that differed in the degree of effortfulness. Participants were asked to attempt simple and choice reaction time variations of two types of attentional task: (1) the combination of two concurrent tasks, and (2) tasks involving decision-making. The authors observed that while control participants performed worse on the dual task conditions, compared to the single task condition, the opposite was true of depressed patients. Moreover, depressed patients were significantly impaired, with regards to both accuracy and timing, on those tasks that involved decision-making processes. It was concluded that the pattern of results indicated a more specific pattern of impairment on effortful tasks and that individuals suffering from

depression may be able to successfully undertake tasks that are effortful in their nature as long as they do not include a decision-making component.

- Speed of information processing

In addition to the proposed deficit in effortful information processing, it has been suggested the depressed patients also experience impairments in the speed of information processing. Evidence of this type of cognitive dysfunction has come from studies that have examined speed of processing during the investigation of depressed patients on a battery of neuropsychological assessments. For example, Austin noted an impairment of information processing speed in a group of melancholic patients using simple and choice reaction time measures, compared to matched controls (Austin et al., 1999). Similarly, Beats and colleagues also observed impaired speed of processing in a sample of elderly depressed patients on a choice reaction time task (Beats et al., 1996).

Information processing speed has also been examined in studies which made no other assessment of cognitive function in depressed patients (e.g. Tsourtos, Thompson & Stough, 2002). Tsourtos and colleagues assessed information processing in patients with MDD and matched controls using an 'inspection time' task. The advantage of the inspection time paradigm is that it provides a measure of speed of processing without the need for a speeded motor response. As with those studies that considered processing speed in conjunction with other cognitive measures, this investigation concluded that patients were indeed impaired on this measure of processing speed. In addition to the use of this simple performance measure, a further advantage of this study was its use of young, unmedicated, unipolar depressed patients. It has previously been suggested that cognitive slowing is only associated with depressive illness in middle aged and elderly individuals (Purcell et al., 1997). However, this latter study provides evidence that impairments traditionally associated only with older depressed patients may in fact be characteristic of major depression irrespective of age.

Mnemonic function

Impairments in mnemonic function have been one of the most frequently investigated and reported deficits in studies of cognitive function in depression (e.g. Austin et al., 1992; Austin et al., 1999; Bazin et al., 1994; Beats et al., 1996; Brand, Jolles & Gispen-de Wied, 1992; Brown et al., 1994; Elliott & Greene, 1992; Elliott et al., 1996; Ilsley et al., 1995; Landro et al.,

2001; Moffoot et al., 1994; Beats et al., 1996; Ravnkilde et al., 2003). Studies have examined performance on a variety of measures of memory function in depressed patients, including verbal and visuospatial measures of both short- and long-term memory. Given the scope of research that has considered mnemonic function in depression, the various subsystems of human memory, and the variety of tasks employed it is advisable to consider the evidence pertaining to each subsystem separately.

(Note: As a result of its close association with others functions that come under the collective title of 'executive function', working memory (WM) function in depression will be discussed in the following sub-section).

- Short-term memory (STM)

'Short-term memory' refers to a passive, limited, and temporary information store (see section 1.2). According to traditional models of human memory, the short-term store facilitates the encoding of information from sensory memory, it's temporary storage, and potential transferral to a long-term memory store (Atkinson & Shiffrin, 1968). Depressed patients commonly report a subjective feeling of dysfunction in their short-term memory. However, the empirical data suggests that there may not be an obvious impairment of the short-term store in MDD.

Despite the subjective ratings of patients samples, there are studies which are indicative of sparing of the short-term memory systems in adults with MDD (e.g. Cohen et al., 1999 Moffoot et al., 1994; Beats et al., 1996; Purcell et al., 1997; Sweeney et al., 2000; Grant et al., 2001). In one study, which compared the profile of cognitive deficit in schizophrenic and depressed patients, individuals with a diagnosis of MDD were found to be unimpaired on two measures of short-term function compared to normal controls, i.e. digit span and word span recall tasks (Cohen et al., 1999). Grant and colleagues observed a similar pattern of results in a larger scale investigation. This study examined STM function on a variety of cognitive tasks, in a sample of more than one hundred depressed outpatients. The authors concluded that there was no evidence of a significant difference between patients and matched controls on measures of both visual and verbal short-term memory (Grant et al., 2001).

Miller also failed to find any significant dysfunction in either verbal or visuospatial STM in a sample of depressed patients, on short-term memory measures of the Luria-Nebraska Neuropsychological Battery (LNNB: Golden et al., 1985; Miller et al., 1991). However, while these findings are in concordance with the studies outlined above, it should be noted that the LNNB was originally designed for use with neurologically impaired patients, and thus may not be sensitive enough to detect cognitive differences between depressed patients and healthy controls. Moreover, as opposed to more traditional neuropsychological batteries, which adopt a qualitative, psychometric approach to assessment, the LNNB is based on a theory of higher cortical functioning. Although the converse may be true, it is possible that adopting such an approach to paradigm may affect the reliability of this measure when used with other clinical populations.

In contrast to these investigations, there are studies which are indicative of a dysfunction of short-term memory associated with major depression (e.g. Wolfe et al., 1987; Miller et al., 1991; Austin et al., 1992; Brand et al., 1992; Brown et al., 1994; Beats et al., 1996; Elliott et al., 1996; Kessing, 1998; Austin et al., 1999; Shah et al., 1999; Moritz et al., 2002; Ravnkilde et al., 2002; Porter et al., 2003). On one hand, there are a number of investigations that have found evidence of a deficit in verbal STM in MDD patients, compared to control participants on a variety of assessments of verbal learning such as the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) (e.g. Wolfe et al., 1987; Miller et al., 1991; Austin et al., 1992; Brown et al., 1994; Austin et al., 1999), the California Verbal Learning Test (CVLT; Delis et al., 1987) (e.g. Elderkin-Thompson et al., 2003), and the Luria Verbal Learning Test (Christensen, 1975) (e.g. Ravnkilde et al., 2002). Thus, suggesting a reliable impairment of verbal STM in MDD.

There are also studies that have noted impairment in the visuospatial short-term store in MDD. In a sample of elderly depressed patients, Beats found evidence of a significant depression related impairment using a battery of tests of visuospatial memory, i.e. pattern and spatial recognition, delayed match-to-sample (DMTS) and paired-associated learning subtests of the CANTAB (Robbins et al., 1994; in Beats et al., 1996). Similarly, Elliott and colleagues also noted deficits on pattern and spatial recognition and DMTS tasks in a group of middle aged, chronically depressed patients, compared to healthy controls (Elliott et al., 1996).

These observations have also been replicated in more specific sub-groups of depressed patients. Indeed, Porter observed a significant difference between medication free patients (i.e. for a minimum period of 6 weeks prior to testing) and a group of matched controls on all of these CANTAB assessments (Porter et al., 2003). Thus, suggesting that impaired short-term visuospatial ability associated with MDD is a manifestation of depressive illness rather than an effect of anti-depressant medication.

The observed disparity in findings between studies regarding short-term memory in MDD may be the result of methodological differences between studies. Therefore, in order to determine whether MDD is associated with an attenuation of STM function it may be more appropriate to examine the findings of meta-analytical or review papers of cognitive function in major depression.

There are a number of articles which have reviewed mnemonic function in MDD (e.g. Cassens, Wolfe & Zola, 1990; Roediger & McDermott, 1992; Burt, Zembar & Neiderehe, 1993; Christensen et al., 1997; Zakzanis, Leach & Kaplan, 1998; Austin, Mitchell & Goodwin, 2001; Porter et al., 2003; Tavares, Drevets & Sahakian, 2003). However, the majority of reviews have either concerned themselves with the various subdivisions in long-term memory or do not make clear distinctions between short- and long-term memory processes in their analysis of relevant studies. Despite this, there are a handful of reviews that have findings pertinent to STM function in major depression.

Cassens reviewed available literature, over a fifteen year period, which had considered cognitive function in depression (Cassens et al., 1990). This review observed that there was evidence of 'significant and reproducible deficits' in learning verbal material and in narrative recall (pp 206). Furthermore, the authors also noted that there was evidence of dysfunction in numerous tests of nonverbal learning, in conjunction with a relative sparing of 'facial recall' (i.e. memory for faces), associated with MDD. However, while evidence was included from studies utilising STM tasks to assess these types of function, the authors did not clearly distinguish between the relative long-term and short-term processes in each of these functions in drawing their conclusions. Therefore, it is difficult to ascertain whether this review is indicative of a significant dysfunction of STM or just of the general processes involved in human memory, such as encoding.

Given the large body of supporting evidence, it seems reasonable to conclude that there is, to some degree, an impairment of both verbal and visual STM associated with MDD. However, given that there is inconsistency in the findings between different studies, it is important that the potential differences between investigations in specific pertinent factors that may contribute to the differences in experimental observations are considered. This issue shall be broached in subsequent sections of this chapter.

- Long-term memory (LTM)

'Long-term memory' traditionally refers to the more permanent storage of information (see section 1.2). While there is considerable debate in cognitive psychology as to the duration and capacity of a LTM store, it is commonly accepted that the memories retained in this store can be characterised as either 'implicit' or 'explicit' memory. Within this model, implicit tasks are defined as those on which performance is not reliant on conscious recollection of a learning event. Explicit tasks, on the other hand, require individuals to consciously recall or remember information that they have previously learned. Research into LTM in major depression has largely focussed on the relative performance of patients on these two sub-types of long-term memory performance.

As opposed to the research literature concerned with short-term memory, the evidence regarding the integrity of long-term memory in MDD is relatively consistent. A number of studies have directly compared the performance of patients with major depression and healthy controls on measures of both implicit and explicit memory and noted an impairment of the latter, but not the former (e.g. Denny & Hunt, 1992; Bazin et al., 1994; Ilsley et al., 1995; Cassens et al., 1990; MacQueen et al., 2002). Moreover, dysfunction in explicit memory in depressed patients has been observed using a variety of different cognitive tasks, including cued and free recall (i.e. Cassens et al., 1990; Denny & Hunt, 1992; Bazin et al., 1994), word-stem completion (i.e. Cassens et al., 1990; Bazin et al., 1994; Ilsley et al., 1995), the Rivermead Behavioural Memory Test (RMBT; Wilson, Cockburn & Baddeley, 1985), and verbal learning assessments, such as the RAVLT (e.g. Wolfe et al., 1987).

The dysfunction in explicit memory has been further demonstrated in a number of review studies, including meta-analytical investigations. Zakzanis and colleagues conducted a meta-analysis of data from 726 depressed patients and 795 matched controls, across a variety

of cognitive tasks (Zakzanis et al., 1998). The experimenters concluded that across tasks the largest effect of MDD on LTM was on measures of encoding and retrieval from episodic memory. Moreover, the effect of MDD on episodic memory function was evident in an array of tasks, including the RAVLT, the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987), the Mattis Dementia Rating Scale (MDRS; Mattis, 1988), and the Rey-Osterrieth Complex Figure (ROCF; Lezak, 1995).

While the majority of studies that have explored explicit memory in depression have used tasks that assess an individual's 'episodic' memory (i.e. the recollection of personally experienced events), there is also alternative form of explicit LTM, i.e. 'semantic memory', that should be considered in assessing the integrity of LTM. Semantic memory, which can be defined as an individual's conceptual knowledge (i.e. knowledge of concepts, rules, and facts), has been considered in a number of studies of MDD (e.g. Wolfe et al., 1987; Austin et al., 1992; Ilsley et al., 1995). However, these studies have all noted that depressed patients were unimpaired on measures of semantic memory, such as oral verbal fluency tasks, compared to matched normal controls.

In contrast to the previous observations, there are investigations that have noted a significant impairment of implicit memory in depressed patients. For example, Elliott and Greene (1992) assessed both explicit and implicit long term memory using four different types of task, i.e. cued and free recall (i.e. explicit memory) and word-stem completion and homophone spelling tasks (i.e. implicit memory). They found that depressed patients were significantly impaired on all of these tasks compared to a sample of healthy normal controls. The authors suggested that these observations might be indicative of a more global pattern of cognitive impairment in major depression than previously thought, or that depression may interfere with 'data-driven' encoding processes. However, it should be noted that this study employed relatively small numbers of participants in each sample (i.e. ten in each) and did not report effect sizes. Therefore, it is possible that the observations in this study may be due anomalies in the data, such as outliers, leading to distortion of the data set as a result of employing small numbers of participants.

In addition to those studies that have investigated the relative effect of depression on implicit and explicit memory, there are a number of studies that have considered the

comparative effect of MDD on visual and verbal long-term memory. Landrø and colleagues compared depressed patients and healthy controls on measures of verbal and non-verbal LTM (i.e. Randt Memory Test; Randt, Brown & Osbourne, 1980; the recurring recognition figures test; Kimura, 1963). The authors found that while depressed individuals were comparatively impaired in their verbal LTM, non-verbal LTM was unimpaired in the depressed sample relative to controls (Landro et al., 2001).

There are also those studies that have failed to find any evidence of any significant deficit in long-term memory associated with major depression (e.g. Grossman et al., 1993; Fossati et al., 1999). Indeed, one study found that, while there was evidence of a significant executive deficit associated with depression, depressed participants were not impaired on any measure of mnemonic function compared to normal controls, including a measure of episodic memory (Grossman et al., 1993).

Therefore, it is reasonable to conclude that there is a significant impairment of LTM associated with major depression, which appears to be limited to episodic explicit memory. However, the contradictions that exist in the literature should be considered in the construction of a model of cognitive function in MDD.

Executive function

'Executive function' is a term that is used to describe a set of functions involved in the ability to initiate and carry out goal-directed behaviour, and includes processes such as attention, concentration, decision-making, planning and working memory (Fuster, 1989). In addition to the considerable quantity of evidence regarding mnemonic function in MDD, a variety of studies have examined the integrity of various processes involved in executive function in individuals suffering from depression (e.g. Channon, Baker & Robertson, 1993; Grossman et al., 1993; Palmer et al., 1996; Channon & Green, 1999; Cohen et al., 1999; Grant et al., 2001; Ravnkilde et al., 2002; Watkins & Brown, 2002; Elderkin-Thompson et al., 2003; Porter et al., 2003).

In order to ascertain an appropriate model of executive processes in depressed individuals it is important to consider their performance on measures of each of the cognitive processes that contributes to executive function.

- Attention

Attention is proposed to be involved in the transfer of information from sensory to short-term memory, and, therefore, is a critical resource for the successful completion of any conscious process (Ashcraft, 1994). Depressed patients will often complain of experiencing impaired attention. Indeed, this type of cognitive dysfunction is so commonplace that impaired concentration has been included as a diagnostic criteria for MDD in DSM-IV (American Psychiatric Association, 1994).

As previously noted, depressed patients appear to be impaired on effortful tasks, i.e. those tasks requiring conscious processing of information. Given the critical association between mechanisms of attention and conscious processing, it is reasonable to suggest that individuals with unipolar depression will be impaired measures of attention. Indeed, there are many investigations that have noted a significant impairment on measures of attention in MDD patients compared to healthy controls (e.g. Miller et al., 1991; Grossman et al., 1993; Trichard et al., 1995; Purcell et al., 1997; Moritz et al., 2002; Ravnkilde et al., 2002; Porter et al., 2003). Investigations of attention in MDD have studied different types of attentional process, including global attentional processes, selective attention, and attentional set-shifting. However, as with most other areas of cognition, the available evidence relating to each of these attentional subtypes is rather contradictory.

A review of investigations of attention in major depression noted that global impairment of attention was associated with MDD, and was most consistently replicated in those investigations using measures of prolonged simple and choice RT, the Continuous Performance Test (CPT: Mirsky et al., 1960) and the Digit Symbol Substitution Test (DSST: Wechsler, 1981; i.e. Mialet, Pope & Yurgelun-Todd, 1996). The authors of this review suggested that impairment on these measures in MDD was indicative of a level of cognitive retardation associated with depressive illness. They also indicated that this type of impairment was often confounded by the psychomotor retardation associated with MDD, and that this confounding effect was evident on those tasks of attention which also have a psychomotor component, e.g. Trail Making Test A and B (Reitan & Wolfson, 1993).

In addition to a global impairment of attention, deficits in selective attention have also been noted in studies of MDD. In their study of elderly depressed patients, Beats and colleagues

employed a visual search task to assess selective attention. They found that depressed patients were significantly impaired on this particular measure, compared to a group of matched healthy controls (Beats et al., 1996). Although it could be argued that the deficit noted in this study may be specific to depression in elderly samples, other studies involving samples of younger adults have also noted deficits in selective attention (e.g. Trichard et al., 1995; Beats et al., 1996; Landro et al., 2001; Moritz et al., 2002). Moreover, in an investigation of cognitive function in unmedicated depressed patients, Porter also found that a depression was associated with a significant deficit in selective attention (Porter et al., 2003).

Studies of attention in MDD have also examined the performance of depressed patients on tests of attentional set-shifting, which are essentially measures of cognitive flexibility. In addition to deficits in global attention function and selective attention, there is evidence to suggest that attentional set-shifting is also significantly impaired in MDD (e.g. Purcell et al., 1997; Merriam et al., 1999; Grant et al., 2001; Moritz et al., 2002). In one investigation of executive function, Channon examined set-shifting ability in dysphoric individuals (i.e. mean score on the BDI = 17.8) using the Wisconsin Card Sorting Test (WCST; Heaton, 1981). It was observed that, compared to normal controls, dysphoric participants made significantly more perseverative and non-perseverative errors on this task (Channon, 1996). Although this study examined dysphoric individuals, rather than a clinical sample, review evidence suggests that the pattern of deficits seen in dysphoric groups is similar, but less severe, than impairment in MDD patients (Hartlage et al., 1993). Moreover, a number of studies of clinically depressed samples have also noted dysfunction in attentional set-shifting. For example, Fossati et al., (1999) used a modified version of the WCST to examine the relative performance of depressed and schizophrenic patients and healthy controls. They found that depressed patients made more perseverative errors on this measure compared to controls, although the difference between the three experimental groups failed to reach significance.

Despite the lack of a significant effect in the latter studies, there are investigations of clinical depressed patients that have observed a significant deficit on this measure in MDD. In a study of cognitive function in MDD, Grant and colleagues found evidence of a significant impairment on the WCST associated with depressive illness in a sample of 123 depressed patients. The authors noted that depressed individuals performed significantly worse than

normal controls on the WCST on a number of performance parameters, including the number of categories completed, perservative responses, perseverative errors, and failure to maintain set. Interestingly, this was the only significant difference the researchers found on a range of measures of cognitive performance between depressed patients and healthy controls (Grant et al., 2001).

Significant differences between depressed individuals and healthy controls on measures of set-shifting have also been noted on assessments other than the WCST. Purcell and colleagues found a relative detriment in the performance of depressed patients on the intradimensional /extradimensional (ID/ED) set-shifting subtest of the CANTAB. In this study only 50% of depressed participants managed to complete all stages of the task successfully, compared to 85% of healthy controls. Moreover, depressed patients required more trials than controls to reach the criterion at the ID shift and ED shift stages of the task. In addition to the comparison of mean percentage of stages completed, the authors also compared the relative performance of depressed and controls participants at each individual stage of the task, including only those participants who met the criterion for the given stage in the analyses. The results of these analyses indicated that depressed and control participants differed only in their performance on the ED shift stage of the task (Purcell et al., 1997). Thus, indicating that set-shifting dysfunction in patients with major depression may be specific to ED shifts only.

Despite the relative consistency of evidence relating to set-shifting in MDD, there are studies which have failed to observe a deficit in this function associated with depression. In another study that employed the ID/ED set shift task, Elliott and colleagues found no significant differences between a sample of patients with major depression and healthy controls on any of the measures of set-shifting (Elliott et al., 1996). Similarly, Sweeney found no significant deficit on the WCST in depressed adults, as compared to normal control participants (Sweeney et al., 2000).

Overall, it appears that MDD is associated with a significant dysfunction in a variety of subtypes of attention, such as selective attention and attentional set-shifting. Moreover, there is evidence to suggest that such deficits are apparent in a range of depressive sub-groups, and across a variety of cognitive assessments. However, impairment of attention

might not be specific to MDD. Indeed a similar pattern of results has been observed in a range of other psychiatric disorders (Mialet et al., 1996). Therefore, attentional dysfunction in major depression may be the result of underlying factors that are common to a range of psychiatric illnesses.

- Decision-making

Decision-making is another component of executive function that is relevant to clinical descriptions of and diagnostic criteria for depressive disorders. Despite the importance of decision-making in models of executive function and depression, there are relatively few studies of cognition in depression that have included specific measures of this function.

Murphy and colleagues considered the relative performance of both MDD and BD patients and a sample of matched controls on a computerised decision-making task (after Rogers et al., 1999a), that was based on a gambling paradigm. On this task participants were required to make probability-based choices and to qualify their choices with an associated 'bet'. Depressed participants (i.e. both MDD and BD) were found to be impaired on the task on a number of parameters, compared to controls. In addition to slower deliberation times, patients failed to accumulate as many points on the task and were more likely to use suboptimal betting strategies (Murphy et al., 2001). Thus, indicating that the deficit in decision-making in major depression is another clinical descriptor that can be empirically measured, and used in the distinction of depressed and normal healthy individuals. However, there is the need for the replication of these findings in order to support this assumption.

- Planning

In studies of cognitive function in MDD one of the most commonly used assessments of planning has been the Tower of London (TOL; Shallice, 1982). As with the other measures of cognitive function that have already been considered, the experimental evidence regarding planning performance in major depression is not entirely consistent.

Deficits in the TOL have been noted in diverse samples of MDD patients, including elderly (Beats et al., 1996) and medication free depressed patients (Porter et al., 2003). Yet, there are a handful of investigations that have failed to find significant deficits associated with MDD

using the TOL task (e.g. Sweeney et al., 2000; Grant et al., 2001). However, it has been suggested that performance on the TOL may be attenuated by the psychomotor component of the task, and both these latter studies both studied samples of depressed patients who did not exhibit psychomotor slowing.

In order to determine the contribution of psychomotor function to the performance of depressed patients on measures of planning ability, Elliott compared the performance of MDD patients and healthy controls on two versions of the TOL, i.e. the original TOL and the new TOL task (NTOL; Owen et al., 1995a). The NTOL task retained the essential features of the TOL but reduced motor demands. In this study it was found that depressed patients were not only impaired on the TOL, i.e. patients exhibited a global deficit in performance accuracy and were slower overall in their planning times, but also showed a deficit in performance on the NTOL, i.e. the mean percentage correct, across all levels of the task, was significantly lower for depressed participants (Elliott et al., 1996). The results of this study confirm the notion that planning on the TOL is to some extent mediated by psychomotor function. More importantly, however, it is also indicative of a planning deficit associated with MDD, which cannot be attributed to depression related psychomotor retardation alone.

- Working memory (WM)

The human working memory system is an active short-term store, which comprised of three components, i.e. the central executive, the phonological loop, and the visuospatial sketchpad (Baddeley & Hitch, 1974; see section 1.2 for a more in-depth account of this model of working memory, and its functional distinctions). Working memory has an integral role in the allocation of processing resources in short-term tasks, and the integration of information from both the long- and short-term stores required for specific task performance. Thus, the processes involved in WM form an essential component of the executive system of human cognition.

It has been suggested that the varied pattern of cognitive impairment observed in major depression may be the result of a faulty allocation of resources, such as would be typical of a dysfunction of the central executive component of working memory (Channon et al., 1993). However, there have been relatively few studies that have specifically considered working

memory in MDD compared to other cognitive processes. Moreover, those studies that have considered working memory in depression have been inconsistent in their observations.

Working memory function can be categorised into two basic forms – i.e. spatial and verbal WM. The most reliable data regarding working memory in MDD appears to come from those studies that have examined verbal WM in depressed individuals. The digit span forwards (DGF) and digit span backwards (DGB) subtests of the WMS-R are two of the more popular assessments that have been used to measure verbal WM in studies of depression. Using both of these measures, one study found that although there was a WM deficit associated with MDD it was only borderline for separating depressed patients and healthy controls (Elderkin-Thompson et al., 2003). Yet, other studies have found significant differences between MDD patients and controls in verbal working memory using both the DGF and DGB (e.g. Fossati et al., 1999, Moffoot et al., 1994, and Moritz et al., 2002).

Examination of verbal WM in MDD has not been limited to studies of DGF and DGB. Landro and colleagues studied verbal WM using the Paced Auditory Serial Addition Test (PASAT; Gronwall & Wrightson, 1975). Participants were assessed using two versions of the PASAT, i.e. a two second interval between the presentation of stimulus items and a four second interval. Depressed participants were found to have significantly lower scores on this measure of verbal WM compared to matched controls (Landro et al., 2001). Thus, supporting the proposal of impaired WM function in major depression.

While the findings relevant to test of verbal working memory appear to be relatively consistent, observations of spatial working memory in MDD are somewhat less reliable. On one hand, those studies that failed in general to find significant differences between depressed patients and healthy normal controls were also unsuccessful in observing any disparity between experimental groups on measures of spatial WM (i.e. Lancaster et al., 1997; Purcell et al., 1997; Sweeney et al., 2000; Grant et al., 2001). Yet, the authors of a number of other studies have noted a discrepancy between the performance of patients and controls on tests of spatial WM. For example, in their study of elderly depressed patients, Beats research group noted that depression was associated with a detriment in performance on measures of spatial working memory taken from the CANTAB neuropsychological test battery (Beats et al., 1996). Correspondingly, Elliott also found impairment on the same

CANTAB measures of spatial WM in a sample of younger adults with major depression (Elliott et al., 1996).

Other researchers have suggested an impairment in spatial working memory associated with MDD which is evident in performance on other spatial measures of executive function, such as the WCST and the TOL (i.e. Elliott et al., 1996; Fossati et al., 1999; Murphy et al., 2003). As previously noted, the use of both of these measures has produced contradictory findings, and performance on each may be confounded by the presence/absence of other dysfunctions of cognition. Therefore, the discrepancy in findings of studies that have considered spatial WM may be linked to the association between this type of working memory and these particular measures of executive function.

Studies that have considered the working memory system by examining either phonological loop or the visuospatial sketchpad function have tended to contemplate its integrity in MDD as a complete system. However, in order to determine whether there is a disruption in the central executive, with relative sparing of the other sub-systems, it is imperative to consider not only the available evidence regarding the working memory system as a whole, but also the findings relating to the integrity of the executive processes of the system. One potential approach to this issue is the examination of the performance of depressed patients on measures that manipulate the central executive.

Although there are not many studies that have considered the executive components of working memory in MDD, Channon and colleagues conducted an exploratory study examining the performance of depressed patients on measures of each element of the working memory system. The experimenters employed three measures of phonological loop function, i.e. phonological similarity and word length effect tasks, and DGF, and a single measure of the integrity of the visuospatial sketchpad, i.e. forward block sequence span (after Milner, 1971). Central executive function, on the other hand, was measured using the backward digit span and block sequence span tasks, the PASAT, the Trail Making tasks, and a letter cancellation test. Although the authors found no significant differences in the performance of depressed and normal individuals on measures of phonological loop or the visuospatial sketchpad function, differences were noted between the experimental groups on measures of central executive function. Patient span was significantly smaller

than controls on the DGB, and there was a trend towards a significant difference between patients and controls on the PASAT (Channon et al., 1993).

Given the lack of pertinent literature, it is difficult to draw reasonable conclusions regarding the integrity of the visuospatial sketchpad and the phonological loop in MDD. Yet, if we are to assume that both the DGB and the PASAT are valid measures of central executive function, the available evidence appears to suggest that there is a reliable impairment of the central executive in patients with MDD. However, although both of these assessments are reliant on working memory, requiring manipulation and recall of information in the short term, it may be the case that the type of working memory being investigated does not adhere to the popular Baddeley and Hitch (1974) model of WM. Indeed, it has been suggested that in the case of the PASAT the function being assessed is closer in nature to the description of WM in the Honig model of working memory (Honig, 1978; in Landro et al., 2001). This model describes WM as a system where the content of a temporary store is continually refreshed and information is discarded once it is no longer of use.

Although the Honig model of working memory has been influential, the Baddeley model has proven to be extremely popular in the study of working memory, in both normal and clinical populations. This popularity may be attributed to evidence from neuroimaging and genetics studies which support the functional distinction between the various components proposed by this model. Consequently, it order to facilitate reasonable conclusions about the integrity of the central executive component of working memory in MDD it may be advantageous to examine WM function using tasks which adequately assess the subcomponents of the Baddeley and Hitch model. This latter point shall be discussed later in this chapter (see section 1.2).

1.1.3.2 Factors affecting the severity of cognitive impairment

Significant differences exist between the methodologies of the various investigations of cognitive function in major depression. Key factors of interest include participant characteristics, the nature of the assessment(s) used, and the function(s) of interest. The functions that have been investigated, and their operational definitions, have been relatively stable between different studies. In addition, the majority of studies considered in this review either used cognitive assessments with established reliability and validity, or

variations based on such tasks. Nevertheless, there are factors of paradigm design that have been shown to be influential in the performance of depressed patients on measures of cognitive function, e.g. the use of feedback and the affective valence of stimulus material. In addition, it would appear that an important source of variance in the observations of different studies is the result of differences in patient characteristics. Common factors of interest to investigators have included participant age, the severity of depressive illness, and medication status.

There are a number of studies that have considered how specific characteristics of experimental design and individual participants are related to participant performance. By considering how these factors have impacted upon the performance of individuals on different measures of cognition it is possible to determine those elements that might be consequential in the differences observed between different studies of cognition in MDD (see Appendix 1A for full list of specified factors of interest in those studies considered for this review).

Motivation

Motivation is a central aspect of depressive illness and as such has previously been considered a key factor in the performance of depressed patients in experimental studies of cognitive function. Indeed, it has been suggested that low motivation is a causal factor in the performance of depressed participants on measures of cognition (Schmand et al., 1994). Evidence from empirical studies of the neuropsychological profile in MDD appears to support this notion (Channon et al., 1993; Beats et al., 1996; Elliott et al., 1997).

However, it is important to note that if motivation were the fundamental factor in impaired cognition in major depression then it would be reasonable to expect a consistent impairment in depressed patients across all tasks. Yet, there is quite clearly evidence of discrepancies in the performance of MDD patients on both the same and different cognitive measures, and a relative sparing of some cognitive functions. Therefore, although motivation is an important factor it cannot singularly account for the profile of cognitive impairment seen in MDD (Elliott, 1998). Resultantly, we need to consider alternative patient characteristics that may aid in the understanding of the types of deficits noted in major depression.

Severity of depression

The level of depressive illness at the time of assessment has been one of the most consistently examined factors. Yet, the currently available data regarding the impact of this characteristic constitute some of the most disjointed findings in the depression literature.

One of the most commonly used measures of severity of depressive illness in experiments is the HRSD. A variety of investigations have observed significant correlations between severity of depression, as determined using the HRSD, and the performance of depressed patients on a range of measures of cognition (e.g. Cohen et al., 1982; Austin et al., 1992; Channon et al., 1993; Austin et al., 1999; Merriam et al., 1999; Sweeney et al., 2000; Grant et al., 2001; Ravnkilde et al., 2002; Elderkin-Thompson et al., 2003). Moreover, other studies have noted that not only does severity of depression correlate with cognitive performance, but it can also account for a significant proportion of the variance in the scores of depressed participants. For example, one study found that the severity of depression, as measured using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) accounted for approximately 28% of the variance in scores of depressed patients on a range of measures.

On the other hand, a number of studies that have failed to find evidence of the association between severity of depression and cognitive performance (e.g. Golinkoff & Sweeney, 1989; Miller et al., 1991; Channon et al., 1993; Channon & Green, 1999; Murphy et al., 1999; Murphy et al., 2001; MacQueen et al., 2002; Moritz et al., 2002). Thus, suggesting that depressive severity may not be associated with cognitive performance, and that cognitive dysfunction in MDD may instead be mediated by other factors that are pertinent to depression.

It is important to note that these contradictory findings cannot simply be explained by differences in the choice of affective assessment, i.e. all the studies listed here used the HRSD. Similarly, the discrepancy does not appear to be related to the presence or absence of cognitive impairment. Indeed a number of studies that have found no association between severity of depression and performance on measures of cognition have found significant differences between depressed patients and controls on the cognitive assessments they employed.

It could be argued that the choice of HRSD may be a key component in the disparity in findings between different studies. The HRSD is an objective measure of depression, which is reliant on the rating of the clinician conducting the interview. Therefore, it is possible that differences between different studies may reflect differences in the assessments of raters in different investigations. However, this is unlikely given the highly structured nature of the HRSD and it's strict scoring guide. Moreover, the same discrepancy in findings has been noted using more subjective measures of affect, such as the BDI. While some studies found a significant correlation between BDI score and cognitive performance (e.g. Cohen et al., 1982; Channon et al., 1993; Grant et al., 2001; MacQueen et al., 2002), others failed to replicate this association (e.g. Channon et al., 1993; Channon & Green, 1999). Given that the examination of the observations of single investigations does not appear to aid in the resolution of this issue, it may be advantageous to consider the conclusions from review and meta-analytical studies.

In a review of cognition in depression, Austin and co-authors argued that there were many studies that demonstrated that cognitive function was independent of severity of depression (Austin et al., 2001). However, in a meta-analysis of studies examining mnemonic function Burt and colleagues found the converse to be true, with both recall and recognition being impacted by the degree of depression (Burt et al., 1993). Moreover, in their meta-analysis of cognitive function in depression, Christensen and colleagues also concluded that severity of depression was correlated with performance (Christensen et al., 1997). In addition, a number of review articles also support the notion of an association between severity of depression and cognitive performance (i.e. Hartlage et al., 1993; Crews & Harrison, 1995; Christensen et al., 1997; Sobin & Sackeim, 1997; Elliott, 1998).

Therefore, it seems reasonable to conclude that performance on a variety of measures of cognitive function in MDD is associated with the severity of depression. This may partially explain some of the inconsistencies in presence or absence of significant cognitive dysfunction between studies. However, it should be noted that the severity of depression appears to only be associated with the severity of cognitive impairment seen in depressed patients, rather than the type of deficit.

Depressive subtype

It has been proposed that there is a differential pattern of cognitive function between individuals with different depressive subtypes. In one investigation, Austin considered the profile of cognitive function in melancholic and non-melancholic depressed patients. Although, melancholic individuals exhibited dysfunction on a range of mnemonic and executive tasks, compared to controls, non-melancholic patients were largely unimpaired on the same measures (Austin et al., 1999). However, a later review by Austin and colleagues concluded that there was little evidence of an association between cognitive performance and subtype of MDD (Austin et al., 2001).

In addition, investigations into the impact of depressive subtype on cognition have also considered the relative performance of 'endogenous' and 'reactive' depressed patients. However, both meta-analytical and review evidence suggested that there are no significant difference between these two types of depressive illness on measures of cognition (i.e. Austin et al., 1992; Crews & Harrison, 1995; Christensen et al., 1997).

Therefore, while some individual investigations of cognition in MDD have noted differences in the cognitive profile of patients with different diagnostic subtypes of depression, across the range of studies considered for this review there is little evidence for this type of distinction. Indeed, it seems likely that the similarities in cognitive profile between different sub-types of depressed patients are more numerous than the differences.

Age

There are two aspects of participant age that are of interest in the performance of depressed patients on cognitive measures, i.e. age at the time of assessment and age at the time of onset of first depressive episode. Although, not all studies have considered the contribution of participant age to the cognitive profile in MDD, there are a handful of studies which suggest that the current age of participants is unimportant in the performance of depressed patients (Austin et al., 1992; Purcell et al., 1997; Austin et al., 1999). However, the conclusions of a number of reviews of cognition in depression are counter-indicative, and seem to support the notion of a significant relationship between the age of participants and cognitive performance. Indeed, a number of review papers have concluded that there is a greater

degree of impairment in older, compared to younger, adult depressed patients (e.g. Austin et al., 1992; Burt et al., 1993; Sobin & Sackeim, 1997; Elliott, 1998).

It has been proposed that the relationship between participant age and level of impairment in depression is not defined by a straight interaction effect. Indeed, Elliott noted that while depressed patients under the age of 40 were more likely to exhibit executive dysfunction, impairment in patients over 50 extended to mnemonic function, with those patients over 70 also exhibiting an additional impairment of cognitive slowing (Elliott, 1998).

Therefore, it can be presumed that the mean age of a given sample of depressed patients will impact upon the observed performance on measures of cognition. Which implies that age is a potentially important factor in explaining the differences in the observations of different empirical investigations of cognition in MDD.

The available data also suggests that the age of the individual at the time of the onset of their first depressive episode does impact upon specific aspects cognitive performance. The association between measures of psychomotor function and onset age appears to be characterised by a significant inverse correlation between these factors. This relationship has been observed in both elderly and younger depressed adults (i.e. Beats et al., 1996; Grant et al., 2001). Moreover, Grant also found a significant correlation between age of onset and performance on measures of executive function (Grant et al., 2001).

These findings may reflect the presence of some factor relating to the age of onset of first depressive episode that is also significant to the presence of specific forms of cognitive dysfunction. Alternatively, it may simply reflect the impact of the total duration of depressive illness. In order to clarify this issue it would be desirable to determine the impact of onset age on measures of cognition in patients who have been matched for total illness duration and number of depressive episodes.

Medication status

(Note: The issue of impact of antidepressant medication on cognition shall be discussed in greater depth in section 1.3 of this chapter)

It is common for depressed patients who participate in experimental investigations to be receiving psychotropic medication at the time of assessment. As a result of the potential confounding effect of medication on patient performance, it is desirable to attempt to ensure that depressed patients are medication free at the time of participation. However, it is not always practically or ethically possible to guarantee this. Therefore, it is important to consider the potential relationship between patient medication status and cognition. Indeed, there is evidence to suggest that some types of medication used to treat MDD may have an impact upon performance on cognitive function – i.e. in both normal and clinical samples (see section 1.3).

There are many investigations that have examined whether there is a significant impairment of cognition in the performance of those patients receiving anti-depressant medication, compared to those who are medication free at the time of testing. One review suggested that the consumption of anti-depressants might have been a confounding factor in the performance of measures of psychomotor function in MDD patients (i.e. Sobin & Sackeim, 1997). However, this conclusion appears to be contradictory to the observations of the majority of individual investigations considered here.

Elliott suggested that, although some more traditional tricyclic medications can disrupt some aspects of cognition, modern anti-depressants have a less noticeable effect (Elliott, 1998). This proposal was supported by evidence from two separate studies by Austin and colleagues (i.e. Austin et al., 1992; Austin et al., 1999). These studies both found a lack of a significant effect of the consumption of anti-depressant medication on cognitive function in depressed patients. Similarly, other investigators have also failed to note a significant impact of anti-depressant medication on cognitive performance in depression, on a range of measures (e.g. Golinkoff & Sweeney, 1989; Purcell et al., 1997; Channon & Green, 1999; Sweeney et al., 2000; MacQueen et al., 2002; Ravnkilde et al., 2002; Murphy et al., 2003).

Based on the currently available evidence it would appear that modern anti-depressant medications have little impact upon the ability of depressed patients to perform cognitive tasks. Moreover, given the proposed relationship between the affective presentation of depressed patients and the degree of cognitive impairment they experience, it can be

speculated that the effect of antidepressant medication on cognitive function in treatment responsive patients may be facilitatory.

Diurnal variation

Diurnal variation in affect is a common aspect of the experience of MDD. This normally takes the form of a lowering of affect in the morning, and an improved mood level in the evening. Given the proposed link between severity of depression and cognition, it has been suggested by some investigators that such variation may have an impact upon the observed pattern of cognitive function in depressed patients.

In order to determine whether this assertion was accurate, Moffoot and colleagues studied the cognitive performance of a group of melancholic depressed patients who had a clear diurnal variation in mood. Participants in this study were assessed in both the morning and the evening on a range of executive and mnemonic tasks. It was found that depressed patients were significantly impaired on a number of assessments, compared to controls, at both assessment times. However, the pattern of impairment seen in patients in the morning was more diverse and severe than the evening pattern (Moffoot et al., 1994). Thus, suggesting that as the mood of depressed patients improved so did their ability to successfully undertake the cognitive tasks.

This study is not the only one to note an effect of diurnal variation on measures of cognition. Porterfield and colleagues also conducted an investigation of the effect of diurnal variation on the performance of a group of patients with a diagnosis of MDD and clear diurnal variation in mood on a range of neuropsychological measures. These authors found that measures of executive function and verbal fluency were sensitive to diurnal changes in mood (Porterfield et al., 1997).

The observation of the effect of diurnal variation has also been observed in more elementary measures of cognitive function. Indeed, in a review of psychomotor function in MDD, Sobin and Sackheim concluded that diurnal variation was significantly associated with the psychomotor performance of depressed patients (Sobin & Sackeim, 1997).

Although the concept of diurnal variation in MDD is intrinsically linked to the notion of severity of depression, the consistency of findings relating to the effect of this factor on observed cognitive performance suggest that its impact may be mediated by factors other than severity alone. For example, Moffoot also noted that the level of impairment in depressed participants was significantly correlated with cortisol levels. Therefore, it may be postulated that cortisol may be an important mediating factor in the observed association between diurnal variation in mood in depressed patients and cognitive function.

Feedback

The use of feedback in cognitive paradigms and its effect upon the performance of depressed patients is linked to the issue of motivation. It has been noted that the nature of feedback given to patients with MDD can have a differential effect on response, compared to normal controls. Depressed patients not only respond less well to positive reinforcement or reward than controls, but also exhibit a tendency to evaluate their performance more negatively. It has been predicted that while control participants will respond to negative feedback with increased motivation, depressed patients are more likely to experience a detriment in motivation or a 'catastrophic reaction' to testing when challenged by negative feedback. This theory of abnormal response to negative feedback in major depression has been supported by evidence from Elliott and colleagues (e.g. Elliott et al., 1997).

However, Elliott's findings have not been replicated in all investigations of the effect of feedback on cognition in depressed patients. Although Shah and colleagues did find evidence of impaired performance on the Delayed and Simultaneous Match to Sample (DMTS and SMTS) subtests of the CANTAB in both depressed and schizophrenic patients, they found no evidence of a motivational effect of negative feedback in controls. Furthermore, there was no indication of an abnormal response to this type of feedback in patient samples (Shah et al., 1999).

Nonetheless, given the critical role of motivation in the performance of depressed participants and the likelihood of this effect of feedback, it is essential to acknowledge the potential effect of the use of paradigms with an intrinsic feedback mechanism in the assessment of cognitive function in MDD.

Affective valence

Another important aspect of paradigm design in investigations of cognition in depression is the hedonic tone of the stimuli that are used. Major depression appears to be associated with a specific deficit in information processing, which is characterised by abnormalities in the processing of mood-congruent material. The empirical evidence is suggestive of a facilitation of the processing of emotionally negative stimuli in major depression, compared to neutral or positive stimuli. However, this type of deficit has been found to be rather specific. Indeed, two separate investigations both found that although the affective valence of stimuli affected the processing of explicit material, implicit tasks were largely unaffected (i.e. Denny & Hunt, 1992; Watkins et al., 1992). In addition, in their review of effortful and automatic processing in depression, Hartlage and colleagues also noted that the degree of impairment on effortful tasks was related to the valence of the stimulus material used in the given task. They concluded that depressed patients exhibited better performance levels on effortful tasks that had used negatively valenced stimuli, compared to positive or neutral stimuli (Hartlage et al., 1993).

Although not all studies have found evidence of this sort of bias in information processing in MDD (e.g. Ilsley et al., 1995), there is considerable support for the notion of the impact of the affective valence of stimuli when assessing depressed patients. Therefore, that the choice of stimuli might impact upon the likelihood of observing significant differences between MDD patients and matched controls on measures of cognition should be noted when considering the evidence of cognitive dysfunction in MDD.

1.1.4 Aetiology of cognitive dysfunction in major depression

Despite a significant degree of inconsistency in the literature which has examined the various aspects of human cognition in those experiencing major depressive illness, there is still considerable evidence to suggest that MDD is associated with a substantial impairment in cognitive function. In addition, is appears that the cognitive profile of depressed patients is mediated by a number of contributory factors. While some of these factors are applicable to a range of psychiatric conditions others appear to be more specific, applying only to those patients with major depression. Although it is imperative to be able to predict the extent of cognitive deficit associated with unipolar depression and the relative importance of those

key factors in patient performance, it is equally important that the aetiology of the profile of cognition in MDD is understood.

One potential approach to the understanding of cognitive dysfunction in major depression is to determine the underlying psychological factors. There are many different psychological theories of depression, which have been developed to aid the understanding of the symptomatic experience of depressed individuals. Although not all psychological accounts of MDD are useful in comprehending the pattern of cognitive impairment seen in depressed patients, some psychological theories do aid in the clarification of cognitive dysfunction in major depression, such as Beck's cognitive theory of depression and Seligman's theory of learned helplessness.

Those psychological theories that are relevant to our comprehension of cognitive dysfunction in major depression do not lend themselves to all aspects of cognitive impairment in MDD, yet are useful in aiding our understanding of some specific deficits. A good example of this is the application of Beck's cognitive theory of depression to the comprehension of biases in information processing associated with major depression. Beck proposed that individuals who became depressed had experienced a predisposition to depressive thinking, and were actively engaged in the maintenance of such thinking. Moreover, he suggested that this predisposition was essential to the formation of depressive 'schemas', and that the activation of these schemas was a causal factor in developing depression (Beck, 1967; Beck, 1976).

The notion of a causal association between a predisposition to negative thinking and depressive illness is also congruent with Bower's network theory (Bower, 1981). Bower proposed that emotions are stored in a semantic network, with each emotion being represented by a single node with numerous connections to other nodes. Within this model, these additional nodes do not just correspond to emotions but instead may represent memories, events, ideas, concepts etc. It was proposed that within this network activation in a single node – via external or internal events – would spread to those nodes with reciprocal connections. Within such a network system the activation of a particular node could, therefore, prime activation in related nodes. In other words, the activation of nodes

corresponding to emotionally negative stimuli may be primed by the experience of depressed mood, given the reciprocal relationship between these two factors.

In addition, to its predictive value in determining the onset of depressive illness and accounting for biases in information processing, Beck's cognitive theory may also be useful in explaining the abnormal response of depressed patients to negative feedback. Beck's theory suggests that individuals with MDD will actively distort external information in a negative fashion, using a variety of processes, e.g. overgeneralization, selective abstraction, catastrophising, and dichotomous thinking. Beck suggested that the negative processing of information was a key factor in the depressed individuals development of negative views of the self, the world, and the future. An essential component of this process is the ability to screen out affirmative information, and to enhance the processing of negative information (Beck, 1967; Beck, 1976).

Psychological theories of major depression are also useful in the explanation of other cognitive dysfunctions that have been observed in unipolar depressed patients, such as deficits in motivation. The importance of motivation in the performance of depressed patients in experimental investigations has already been noted in this review. Indeed, motivation appears to be an essential factor in cognitive performance in MDD.

Motivational deficits may be partially explained by Seligman's theory of learned helplessness (Seligman, 1975). Seligman proposed that depressed individuals anticipate the occurrence of negative events but not positive ones, and believe such events to be inevitable, and, therefore, feel incapable of preventing such events from happening. Seligman also suggested that those who suffer from depression would attribute blame for adverse events to internal, fixed causes, rather than external, changeable ones. Within this framework motivational deficit in depression may be determined by the feeling of inability to alter ones circumstances that is experienced by depressed individuals. Furthermore, as the level of importance of an uncontrollable event increases the level of control perceived by the individual will decrease, thus leading to a greater depressive reaction – i.e. reduced motivation.

Although psychological approaches are useful in assisting in our understanding of causal factors in aspects of cognitive abnormality in MDD, there are still many gaps in our understanding of the processes underlying such behavioural deficits. Moreover, such theories do not account for full scope of cognitive dysfunction noted in depressed patients. Therefore, it may be advantageous to consider alternative models of depressive symptomology that can more appropriately account for the complexity of the experimental evidence in this field, such as the neuropsychological approach.

1.1.5 Neuropsychological profile in major depression

Neuropsychological approaches to the understanding of depressive symptomology provide an alternative, but complementary, approach to the psychological theories of major depression. These approaches are concerned with the association between observable behaviour and underlying biological causes, and purport that the cognitive dysfunctions in MDD can largely be attributed to the manifestations of abnormalities in the structure and functioning of regions of cortex postulated to be involved in specific aspects of cognitive function.

Evidence for impaired regions of activation in depression comes from a number of sources. Firstly, there is the evidence of the cortical activation associated with performance of cognitive tasks that depressed individuals have been noted to be impaired on in normal healthy adults. Additional evidence also arises from comparison between cognitive deficits seen in clinical groups with known structural abnormalities and similar performance profiles in depressed patients. However, a more direct approach to the understanding of neuropsychological function in depressed patients is the examination of evidence from neuroimaging studies of depression.

1.1.5.1 Neuroimaging and major depression

There is considerable range of neuroimaging investigations that have been concerned with major depression, ranging from the examination of brain structure in MDD at a cellular level to studies of gross brain function. It is proposed that in order to ascertain an accurate neuropsychological model of brain function one must contemplate the available data relating to both structural and functional brain imaging in depression.

1.1.5.1.1 Structural deficits in depression

The first structural imaging study of mood disordered patients was a computerised tomography (CT) study, which was conducted by Jacoby and Levi (i.e. Jacoby & Levi, 1981). Rangel-Guerra and colleagues conducted the first magnetic resonance imaging (MRI) study of depression a couple of years later (i.e. Rangel-Guerra et al., 1983). The introduction of MRI brought about significant changes in structural imaging, including the ability to produce high-resolution images with more accurate structural localisations. Moreover, it allowed for an improvement in the qualitative volumetric analysis of both cortical and subcortical gray matter (Soares & Mann, 1997).

In a review of structural neuroimaging studies of mood disorders (i.e. both MDD and BD) Soares and Mann suggested that the prefrontal cortex (PFC) played an integral role in cognitive dysfunction and the modulation of mood in depression, as a result of its extensive connections to both cortical and subcortical regions. More specifically, they proposed that a network involving a limbic-thalamic-cortical circuit, consisting of the medial and ventrolateral PFC, the amygdala, and the mediodorsal nucleus of the thalamus, and a limbic-striatal-pallidal-thalamic circuit, involving the striatum and the ventral pallidum underlay the pathophysiology of mood disorders (Soares & Mann, 1997; see Figure 1.1).

Soares and Mann considered structural neuroimaging evidence of both generalised and regional brain abnormalities in patients with affective disorders in order to determine whether their proposed model of PFC involvement in the symptom presentation in depression was accurate. In the case of unipolar depressed patients the most consistent observations were of reduced cortical volume in frontal lobe (FL), cerebellum, caudate, and putamen. Although their findings did support the proposed neuroanatomic model of mood regulation, they suggested that further examination of the clinical and biological correlates of these structural changes was required in order to develop a more inclusive model.

Support for the Soares and Mann model of structural deficits associated with depressive illness came from a later review of 3D MRI studies of neuroanatomic changes in unipolar depression by Sheline (i.e. Sheline, 2000). This review noted that changes in cortical structure associated with early onset depression in the hippocampus, amygdala, caudate nucleus, putamen, and frontal cortex. Thus, supporting the notion of a fronto-striatal deficit

in MDD predicted by the Soares and Mann model. It was proposed that this pattern of tissue loss could have resulted from a number of mechanisms, including: neuronal cell loss through repeated exposure to episodes of hypercortisolemia; increased vulnerability to glutamate neurotoxicity, as a result of glial cell loss; and reduction in neurotrophic factors and in cortical neurogenesis resulting from increased level of stress. This review also considered the persistence of these types of structural deficit and found that the only deficit to persist beyond resolution of depressive symptoms was volume loss in the hippocampus.

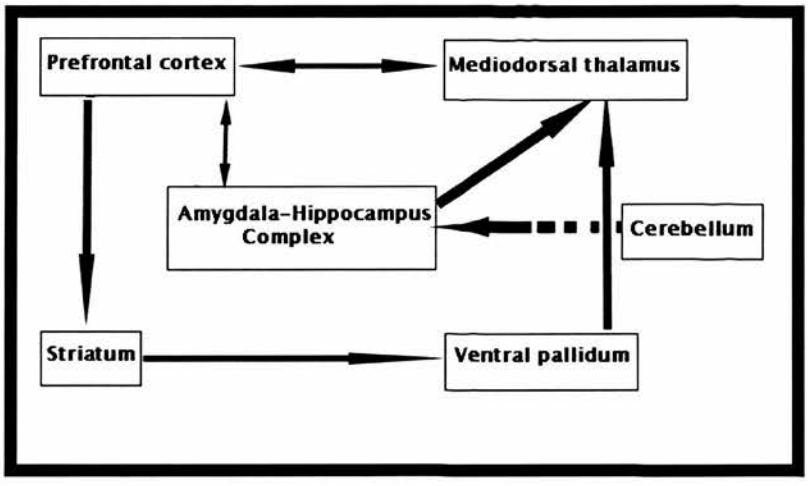

Figure 1.1: Soares and Mann (1997) neuroanatomical model of mood regulation

However, the pattern of structural impairment implied by both of these review articles may not be consistent across sub-groups of depressed patients. Indeed, recent evidence suggests that the integrity of cortical structures may be associated with patient outcome. Shah and colleagues examined structural MRI scans of twenty patients suffering from chronic, treatment-resistant major depression. Using voxel-based analysis, the structural scans of this group were compared to those of recovered patients and healthy controls. In addition to subtle changes in the left hippocampus, right fronto-striatal atrophy was observed in the treatment-resistant patients, but not in other groups. Furthermore, the degree of atrophy noted in patients was correlated with the cumulative number of electroconvulsive therapy (ECT) treatment received. Thus, suggesting that this type of structural deficit was not necessarily a causal factor in depressive illness, but instead may have been acquired and related to the severity of depression (Shah et al., 2002).

These findings were an extension of an earlier study by Shah and colleagues, which also highlighted the importance of structural deficits in major depression (i.e. Shah et al., 1998). In this earlier study MRI structural images of chronic treatment resistant depressed patients - who were characterised by a period of MDD lasting two years or more - and healthy controls were compared for evidence of depression associated structural deficits. The results of a voxel-by-voxel analysis of participants' brain images revealed reduced gray matter density in the left temporal cortex, in a region that included the hippocampus in depressed patients. In addition, there was also a depression associated trend towards reduced density in the right hippocampus. Moreover, the authors also noted a significant correlation between the density of the left hippocampus and the performance of depressed patients on a measure of verbal memory (Shah et al., 1998). Thus, suggesting that structural deficits may be of functional and behavioural significance in MDD.

There is also evidence to suggest that the relationship between structural deficit and depressive symptoms is not only apparent in adults with MDD. Steingard used volumetric analysis to compare the MRI scans of depressed children and adolescents to those of non-depressed psychiatric controls. The investigators examined the frontal lobe, lateral ventricular, and total cerebral volumes (FLV, VV, and CV) and, as a result of individual differences in head and body size, compared experimental groups for differences in the ratios of FLV/CV and VV/CV. Depressed participants were found to have significantly smaller FLV/CV and significantly larger VV/CV ratios. The pattern of decreased frontal lobe volume in the depressed children was similar to that seen in depressed adults. These findings indicate that this region might play a role in the pathogenesis of early onset depression (Steingard et al., 1996).

Although there is relatively consistent evidence regarding the nature of structural deficits associated with MDD, this latter study raises the question of whether the structural changes seen in depressed individuals are causal factors in depressive illness? Certainly, both of the review articles of structural imaging in affective disorders considered here suggest that, with the exception of hippocampal volume, those cortical changes seen in depressed patients disappear upon recovery. Moreover, the studies conducted by Shah are indicative of persistent deficits only in those patients who experience chronic, treatment-resistant depression, i.e. no persistent differences were noted between recovered patients and healthy

controls. Based on these observations one could suggest that if such structural deficits only persist during the course of an individual's depression then they may be a result of MDD, rather than a causal factor. However, determining the nature of the relationship between major depression and specific structural abnormalities is complex, and is reliant on the provision of evidence of structural deficits preceding the onset of depression.

It has been noted that lesions in particular cortical regions as a result of stroke, for example, can precipitate the onset of affective disorders. Indeed, epidemiological data from across the world indicates that prevalence rates for MDD post-stroke are 19.3% among in-patients and 23.3% for outpatients (Robinson, 2003). Although some studies have failed to find a significant association between lesion location and affective disorder, a recent meta-analysis which examined the lesion location and time since the incidence of stroke found that in the 2 months following an acute stroke left frontal and left basal ganglia lesions were significantly more frequent in those patients presenting with major depression ((i.e. Robinson, in press; cited in Robinson, 2003). Similarly, another meta-analysis by Narushima and colleagues found a significant correlation between the severity of depression in poststroke patients and the proximity of the lesion to the frontal pole in patients with left hemisphere stroke (Narushima, Kosier & Robinson, 2003). As with the previously presented findings, both of these studies are indicative of structural deficits in frontal and striatal regions of cortex in depressed individuals, which may be associated with the presentation of depressive symptoms.

As there is a potential causal link between the regions of structural abnormality and cognitive deficits in MDD, the presence of structural deficits in patients with major depression is not only of concern in the affective presentation of depressed patients, but is also of interest in understanding the model of cognitive dysfunction in MDD. However, it is not sufficient to infer this sort of association in the absence of evidence to suggest that the regions that show structural dysfunction in MDD and are indeed associated with cognitive function in normal healthy adults are functionally abnormal in unipolar depression.

1.1.5.1.2 Functional deficits in depression

In addition to structural imaging studies, functional neuroimaging has also been used to explore the pathophysiology of unipolar depression. Generally speaking there are two

approaches to the non-invasive imaging of brain function: electrophysiological methods and metabolic/vascular methods. Recent research into neural function in major depression has focussed largely on the latter approach, using a range of metabolic imaging techniques such as functional MRI (fMRI), positron emission tomography (PET), and single photon emission computerised tomography (SPECT). Using these imaging methods, investigators have conducted two general types of examination of brain function, i.e. 'resting state' and 'activation' studies. Resting state investigations are those studies that examine regions of cortical activation while patients are inactive, or 'at rest'. Activation studies, on the other hand, consider the pattern of activation during performance of a specific cognitive task. By considering evidence from both approaches it is possible to determine an accurate model of cortical function in major depression.

(Note: A summary of the observations from resting state and activation studies of brain function associated with MDD considered for this review can be seen in Appendices 1C and 1D).

Resting state studies

Using either PET or SPECT in conjunction with a variety of different paradigm approaches, resting state investigations of brain function have identified a number of regions of abnormal cortical activation in studies of depressed patients. While some studies have simply compared resting state activations in depressed patients and healthy controls, other studies have considered the differences in function between individuals during depressed episodes and periods of remission. There are also those investigations that have considered the association between the performance of depressed patients on a given cognitive task and resting state activation.

While there are studies of resting state blood flow that have implied a reduction in global flow in depressed patients (e.g. Sackeim et al., 1990), there is evidence to suggest that the profile of cognitive dysfunction in MDD is the result of more localised abnormalities. Indeed, across investigations there appears to be evidence of a dysfunction in frontal subcortical circuitry (Elliott, 1998). This assertion can be qualified by examining the available evidence from the various research groups who have been involved in resting state imaging studies of MDD.

Bench and colleagues, for example, employed PET to consider resting regional cerebral blood flow (rCBF) in a sample of forty individuals with a diagnosis of major depression, and compared the acquired images to those of a group of matched healthy controls (i.e. Bench et al., 1992; Bench et al., 1993). It was observed that in contrast to controls, depressed patients exhibited a relative decrease in rCBF in the left anterior cingulate (AC) and left dorsolateral prefrontal cortex (DLPFC). Patients also showed tendency towards decreased blood flow in the left angular gyrus and increased blood flow in the left posterior cingulate cortex.

In addition to investigating the mean blood flow differences between patients and controls, Bench also considered the relationship between the functional abnormalities associated with MDD and symptom presentation. In order to do this the authors identified three factors of interest, which had loadings for anxiety, psychomotor dysfunction, and cognitive performance. It was found that anxiety was positively correlated with blood flow in the posterior cingulate and the inferior parietal lobule bilaterally, whereas psychomotor retardation correlated negatively with rCBF in the left hemisphere in DLPFC and the angular gyrus. Furthermore, cognitive performance was correlated positively with the level of blood flow in the left medial prefrontal cortex (Bench et al., 1992; Bench et al., 1993). Therefore, these studies not only implied that there was an abnormal pattern of cortical activation associated with MDD, but that specific abnormalities in regional blood flow may be linked to specific aspects of depressive symptomology.

This pattern of cortical dysfunction has also been noted in other series of PET studies. The Danish PET/depression project have also examined the association between neuropsychological function and cerebral blood flow in major depression in a series of investigations (e.g. Soares & Mann, 1997; Videbech et al., 2001; Videbech et al., 2002; Ravnkilde et al., 2003). A series of studies by this research group have found a significant increase in blood flow in the right hippocampus and the left cerebellum in depressed patients, compared to controls, in conjunction with a trend towards increased in rCBF in the left lateral occipito-temporal gyrus (Videbech et al., 2001). Moreover, further analysis of resting state blood flow also revealed an increase in the AC gyrus and the basal ganglia in patients with MDD (Videbech et al., 2002).

The Danish PET/depression project also extended their analyses in order to examine the relationship between abnormalities in blood flow and cognitive function in depression (i.e. Ravnkilde et al., 2003). In these studies, participants were asked to complete a battery of neuropsychological assessments, which the experimenters then used to extract a set of principal components: i.e. general ability; attention; verbal memory; visual memory; language; and executive function. Multiple linear regression analyses were then used to determine whether there was a correlation between these components and blood flow in selected regions of interest. The only significant correlations between cognitive components and blood flow for patients were for general ability (i.e. positive correlation with bilateral hippocampal function) and executive function (i.e. positive correlation in right temporal cortex and right AC). However, significant differences in correlations with blood flow between patients and controls were noted for general ability (i.e. right orbitofrontal cortex and bilateral hippocampus), attention (i.e. anterior cingulate), visual memory (i.e. left posterior cingulate), and language (right prefrontal cortex). The authors concluded that the cognitive deficits they had noted in the depressed sample were not associated with the rCBF of the anatomical structures that were affected in this group, and therefore that cognitive dysfunction in depression was not related to specific locations in the brain as with normal cognition.

Other resting state studies have also found evidence of an association between measures of cognition and resting blood flow. In two separate studies, Dolan and colleagues observed a reduced rCBF in the DLPFC, bilaterally and the left AC in patients with depressive disorders (i.e. Dolan et al., 1992; Dolan et al., 1993). Moreover, in the first of these investigations it was found that cognitive impairment in depression was associated with decreased blood flow in the left anterior medial PFC, in conjunction with increased blood flow in the cerebellar vermis. This data appears to suggest that there is a pattern of functional abnormality that is specific to the type of cognitive impairment observed in major depression. However, as with the pattern of cognitive dysfunction in MDD it is possible that blood flow abnormalities may not be specific to depression, but instead may reflect dysfunctions that are common to other psychiatric disorders.

In an attempt to answer whether the rCBF abnormalities that had been documented in studies of MDD were specific to depression or the type of cognitive dysfunction, Dolan

compared the regional cerebral blood flow of depressed and schizophrenic individuals with a deficit in psychomotor function, i.e. poverty of speech. It was found that psychomotor retardation was associated with significantly lower rCBF in DLPFC, independent of diagnosis (Dolan et al., 1993). Thus, implying that blood flow abnormalities may be associated with the nature of cognitive dysfunction rather than depression per se.

Abnormalities in blood flow in major depression have not only been noted in frontal cortex, there is also evidence to suggest striatal dysfunction in major depression. As already noted, the Danish PET/depression project found evidence of increased blood flow in the basal ganglia in depressed patients (Videbech et al., 2002). In addition to the findings of this research group, an early study of frontal cortex and basal ganglia metabolism in affective disorders found that unipolar depression was associated with a decreased metabolic rate in the basal ganglia (Buchsbaum et al., 1986). Although, this observation should be treated cautiously given the relatively small number of unipolar depressed patients who participated in the study (i.e. N = 4). Nonetheless, there is additional evidence to suggest striatal dysfunction in MDD. In a comparison of the relative blood flow in MDD and obsessive-compulsive disorder (OCD), Saxena and colleagues found that a combined diagnosis of MDD and OCD was associated with significantly lower metabolism in the caudate than in OCD alone (Saxena et al., 2001). However, it is possible that in this particular study dysfunction in cerebral blood flow may have been the result of a factor resulting from the dual diagnosis, rather than a contributory factor of MDD.

While there is considerable evidence of abnormalities in resting state blood flow in MDD, a key factor in our understanding of the pathophysiology of depression is whether such deficits are state or trait factors. In order to address this issue, some studies have investigated resting rCBF in individuals who have recovered from depression. In a follow up to their original investigations, Bench and colleagues identified and re-scanned twenty five of the original sample of depressed patients who participated in the study and had experienced clinical remission (Bench, Frackowiak & Dolan, 1995). The authors compared recovered patients to samples of both depressed and healthy control participants. They found that remission was associated with a significant increase in rCBF in the left DLPFC and medial prefrontal cortex (PFC), including AC. Although there was a relative increase in the blood flow in the angular gyrus the effect disappeared when depressed and recovered

patients were matched for medication status. Therefore, this series of investigations implies a level of frontal dysfunction in blood flow in the frontal cortex in MDD, which is associated with symptom severity and appears to be state (rather than trait) related.

Tutus and colleagues also examined the effect of remission from major depression on regional cerebral blood flow. Using SPECT, these authors examined the profile of blood flow in unipolar (i.e. N = 10) and bipolar (i.e. N = 7) patients, who met the DSM-IV criteria for a MDE, during depressed and remitted episodes. During depressed episodes unipolar depressed patients showed a relative increase in rCBF in the left frontal cortex compared to both bipolar and healthy controls subjects. However, these differences in cortical metabolism disappeared upon remission. Thus, supporting the notion that resting state blood flow abnormalities in MDD are a state, rather than trait, aspect of depressive illness (Tutus et al., 1998). Yet, the differences between observed blood flow in unipolar and bipolar patients suggests that these state abnormalities may be specific to episodes of major depression in MDD only.

In summary, resting state studies of rCBF in MDD appear to consistently implicate a significant dysfunction in blood flow in a number of frontal and striatal regions during episodes of major depression. Thus, supporting the notion of impaired fronto-striatal circuitry in major depression. Moreover, frontal dysfunction appears to most reliably noted in areas which constitute the medial prefrontal cortex. This region has a number of primary projections to other cortical regions, including striatal areas, which are involved in a number of both affective and cognitive processes in normal healthy adults (Elliott, 1998: see Figure 1.2). Therefore, abnormal blood flow in the frontal lobes in depressed patients may be a causal factor in dysfunction in fronto-striatal circuitry, and in the affective and cognitive symptoms in MDD.

Although these abnormalities have been shown to correlate with cognitive dysfunction in depression, there is evidence to suggest localised blood flow dysfunctions in MDD may not be directly associated with specific aspects of cognition. Moreover, deficits in cerebral blood flow may not be attributable to MDD but instead may reflect the presence of certain symptoms of depression, which are common to other psychiatric illnesses. Finally, resting

state studies support the theory that blood flow dysfunctions in MDD are a state aspect of the disorder.

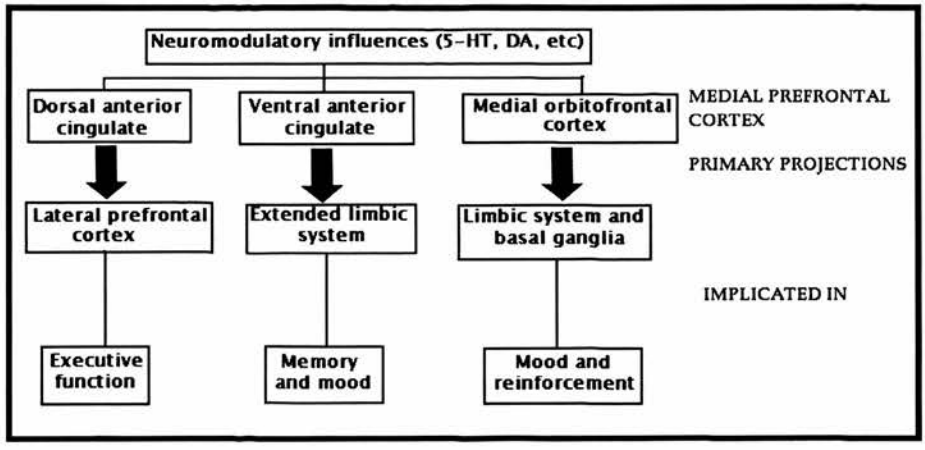

Figure 1.2: Elliott's (1998) model of the role of medial prefrontal cortex in the presentation of symptoms in major depression.

- Factors affecting resting state blood flow in major depression

Similar to the profile of cognitive dysfunction seen in MDD, there are a number of potentially confounding factors that have been proposed to impact upon cerebral metabolic rate in depressed patients. Common factors of interest in resting state studies of MDD have included severity of depression (e.g. Mathew et al., 1980; Sackeim et al., 1990; Austin et al., 1992; Tutus et al., 1998; Saxena et al., 2001; Videbech et al., 2001; Skaf et al., 2002; Videbech et al., 2002) and medication status (e.g. Sackeim et al., 1990; Bench et al., 1992; Dolan et al., 1992; Bench et al., 1993; Saxena et al., 2001; Videbech et al., 2001). Although there is reasonable reliability in the regions of abnormal blood flow associated with depression identified across studies, the confounding effect of such factors is not consistently evident.

In two separate investigations using ^{133}Xenon inhalation it was found that brain metabolism was associated with severity of depression, as measured using the HRSD (i.e. Mathew et al., 1980; Sackeim et al., 1990). The first of these investigations noted a significant inverse correlation between HRSD score and rCBF values in a sample of depressed patients. Furthermore, the latter study found that the extent of topographic abnormality in depressed participants was significantly associated with severity of depression.

A similar pattern of results has been noted in other studies of resting state blood flow in depression. For example, in a PET investigation of brain metabolism in MDD, Saxena found that HRSD score was negatively correlated with rCBF in the hippocampus and amygdala (Saxena et al., 2001). Whereas, Skaf and colleagues noted that severity of depression was associated with metabolic rate in the right dorsal AC (Skaf et al., 2002).

However, not all studies have found evidence of an association between the severity of depression and measures of cerebral metabolism. There are both SPECT and PET examinations of blood flow in depression which have failed to find any significant relationship between severity of depression and metabolic rate (e.g. Tutus et al., 1998; Videbech et al., 2001).

A number of resting state studies that have considered medication status appear to support the notion that medication is unimportant in resting blood flow in depressed patients. Bench concluded that there were no significant differences between medicated and unmedicated patients in global blood flow or in blood flow in those regions that had been identified as being significantly associated with major depression (Bench et al., 1992; Bench et al., 1993). However, they did note a trend towards a relative decrease in flow in the medicated group in the right inferior frontal lobe. Similarly, irrespective of presence of cognitive impairment, Dolan also noted that medication status had no effect on resting blood flow in depressed patients (Dolan et al., 1992).

Activation studies

Resting state studies have been, and still are, important in the provision of information relevant to the understanding of the pathogenesis of cognitive dysfunction in depression. Nonetheless, the inference of a causal link between cognitive and metabolic abnormalities in such studies may be flawed as a result of the fact that measures of cognition and blood flow are not made simultaneously. While these factors may be correlated it is possible that the changes in blood flow reflect some changes in another, possibly unknown or unrelated, factor. Functional activation approaches to neuroimaging partially resolve this issue. Although there is still the possibility of the confounding effect of some unknown factor, the fact that measures of cognitive performance and brain metabolism are made at the same

time allows for more accurate temporal and spatial localisation of regions of activation associated with specific cognitive profiles.

Functional activation studies of depression have mainly used either PET or blood oxygenation level dependent (BOLD) functional MRI to examine cortical activation during the performance of cognitive measures. Despite the variety of cognitive dysfunctions that have been noted in patients with major depression, the majority of studies appear to have focussed on tasks that are likely to be reliant on those areas of cortex thought to be functionally abnormal in MDD, such as measures of executive function and verbal fluency.

- Functional neuroimaging of verbal fluency

There have been two recent neuroimaging investigations of verbal fluency in MDD. The first of these two studies (i.e. Okada et al., 2003) employed BOLD fMRI to assess cortical activation during performance of a standard measure of verbal fluency. Depressed individuals were found to be significantly impaired upon the verbal fluency task, compared to healthy controls, in terms of the number of words generated. The effect of participant group was also apparent in the level of cortical activation seen in participants, i.e. activation in the left PFC was severely attenuated in the depressed patients compared to controls.

The second of these investigations (i.e. Videbech et al., 2003) also found an impairment of verbal fluency associated with major depression. However, the researchers involved in this study failed to find any significant differences in regions of cortical activation between patients and normal controls. Both groups activated a network of regions encompassing the left AC, left DLPFC, left medial PFC, and right cerebellum during performance of the task, yet there was no significant difference in the level of activation of these regions between experimental groups.

This latter investigation contrasts significantly with the observations of resting state studies, which have shown significant abnormalities in these regions in samples of depressed patients compared to normal controls. Assuming that the evidence from resting-state studies is reliable, then there are a number of explanations for the lack of a significant difference in this study. For example, there may be differences between the pattern and magnitude of cortical activation in patients and controls but they may be too small to detect,

or they may be masked by the contribution of individual differences in either experimental group. Alternatively, it may be the case that under situations of sufficient difficulty patients are able to increase the level of activation of regions of cortex necessary to perform the task at hand.

- Functional neuroimaging of executive function

There are a variety of neuroimaging studies of MDD that have examined brain metabolism associated with the performance of a range of measures of executive function, including planning, set-shifting, response inhibition, and working memory (i.e. both verbal and spatial).

Elliott and colleagues investigated cortical metabolism associated with a test of planning (i.e. the TOL task) using PET, in two separate investigations (i.e. Elliott et al., 1997; Elliott et al., 1998). In the first of these investigations depressed patients were found to be significantly impaired on the TOL task in terms of accuracy, but not reaction time, compared to a group of matched healthy controls. In addition, the increase in difficulty experienced by patients was disproportionate to task difficulty. The differences in behavioural performance in this study were reflected in significant differences between depressed patients and control participants in rCBF. During task performance controls engaged a network of PFC, AC, posterior cortical areas and subcortical structures (including the striatum). Patients, on the other hand, failed to show significant activation in both the cingulate and the striatum. Additionally, activation in other prefrontal and posterior regions was severely attenuated in patients, relative to controls. Moreover, patients did not exhibit the augmentation of activation in the caudate nucleus, and right PFC that was associated with increased task difficulty in control participants.

In the second of these two investigations the authors again examined TOL performance during PET scanning. However, this time the experimental procedure was altered to include a 'guessing' task. Both tasks were administered under three different experimental feedback conditions, i.e. positive, negative, and neutral. Patients' overall accuracy was significantly lower than controls, and both groups performed worse in the negative feedback condition than in the positive condition. However, under neutral feedback conditions the performance of controls was most similar to the positive condition, whereas the patients performance

profiles was more akin to performance in the negative condition. In addition to these behavioural differences, these experimental manipulations resulted in significant differences in rCBF between patients and controls in the medial caudate and the ventromedial orbitofrontal cortex. Moreover, activity in depressed patients was lower overall, and they failed to show the differential response to the different feedback conditions that was noted in the control group. Therefore, the results of both investigations by Elliott and colleagues support the notion of impaired frontal and striatal function in MDD, and are indicative of an association between fronto-striatal dysfunction and impairments on measures of planning ability.

It was previously noted in this review that some researchers have observed differences in the performance of depressed patients and normal controls on measures of attentional set-shifting, such as the WCST. However, not all studies have found dysfunction on this measure in MDD. Moreover, in those studies that have failed to find a depression associated deficit on the WCST there also appears to be a lack of metabolic differences between depressed patients and healthy controls. In an investigation of proposed 'hypofrontality' in schizophrenia and depression, Berman examined the relative performance of depressed and schizophrenic patients, and healthy controls on the WCST, during functional neuroimaging (i.e. ^{133}Xenon inhalation). In this investigation the performance of patients did not differ significantly from controls on any parameter of the task. Accordingly, there were no significant differences in either global or regional flow between patients and controls (Berman et al., 1993). Although this observation is in contradiction to both cognitive and neuroimaging studies of MDD, it is possible that the relatively small number of depressed patients (i.e. N = 10) had an effect on the statistical power of this study, and, therefore, may have impacted upon the findings.

Another example of executive function that has been studied in functional neuroimaging investigations of MDD is 'response inhibition'. Kaiser and colleagues investigated this particular cognitive function using an auditory 'Go'/'No-go' task. In contrast to the other studies mentioned in this review, this particular investigation involved electrophysiological neuroimaging method, i.e. high-resolution electroencephalography (EEG). The authors found that while there was no difference between depressed patients and controls on the 'Go' task conditions, patients were impaired on the 'No-go' conditions. Thus, the

behavioural findings were indicative of impairment in response inhibition in MDD. This impairment was accompanied by a reduction in the early fronto-temporal positivity in the N2 time window, which was associated with performance of the 'No-go' task in controls. Therefore, the results of this study are suggestive of a dysfunctional activation of the network that normally subserves executive control (Kaiser et al., 2003).

Data relating to the functional neuroimaging of working memory in MDD is of particular relevance to the current series of investigations. There are two studies that have specifically considered WM function in major depression. Firstly, a study by Barch and colleagues examined the performance of depressed, schizophrenic, and healthy controls on a 2-back working memory task, during acquisition of BOLD fMRI sequences (Barch et al., 2003). Whereas, Pelsoi compared the performance of individuals with MDD and healthy controls on the Sternberg working memory task (Sternberg, 1966) during EEG (Pelosi et al., 2000).

In the latter of these two studies, Pelsoi found that depressed patients made significantly more mistakes as the memory load of the task was increased from one item to five items, compared to controls. In addition, there were significant differences in the response patterns of event-related potentials (ERP's) of patients and controls. The abnormalities that were noted by the authors were suggestive of abnormal sensory/perceptual processing in MDD, which the authors inferred was the result of deficits in selective attention mechanisms. Moreover, the nature of ERP dysfunction seen in depressed patients was indicative of compensatory mechanisms or a dysfunction of inhibitory systems. Given that the types of abnormalities seen in patients were sensitive to memory load, the researchers suggested that they might reflect alterations of memory related processes.

Barch and colleagues, on the other hand, investigated both verbal and visual working memory function by using both words and faces as stimulus items on a 2-back variation of the n-back paradigm. The authors found that depressed patients were unimpaired on both verbal and visual versions of this WM task, compared to controls. However, despite the lack of behavioural differences on these measures, controls demonstrated significantly higher activation than depressed patients in bilateral thalamus, right precentral gyrus, and right parietal cortex in response to both experimental conditions. While controls showed task related activation for words, but not faces, in the right middle-temporal gyrus and right

superior frontal gyrus, patients exhibited the opposite pattern of activation. Therefore, although the results of this study are indicative of sparing of both verbal and visual working memory in MDD, there is evidence of depression related dysfunction in regions of cortex associated with WM function in normal healthy adults (see section 1.2).

Executive dysfunctions in depressed patients have also been observed on measures of sustained attention. Kimbrell recently studied brain activation associated with sustained attention in MDD using fluorine-18-deoxy-glucose (^{18}FDG) PET, in a sample of depressed patients whose diagnoses ranged from euthymic to severely depressed. Depressed patients and healthy controls both completed an auditory continuous performance test. Although patient's performance was similar to controls on measures of accuracy, depression was associated with slower reaction times. It was observed that severely depressed patients showed a decrease in regional cerebral glucose metabolism (rCRMglu) in the right hemisphere in PFC and paralimbic/amygdala regions, and bilaterally in the insula and temporoparietal cortex (i.e. rCRMglu right hemisphere > left). Furthermore, they also exhibited increased metabolic activity bilaterally in the cerebellum, lingula/cuneus, and brain stem. However, given the lack of significant group differences in accuracy measures, it is possible that the differences in glucose metabolism are simply a reflection of differences in psychomotor function (Kimbrell et al., 2002). Alternatively, the lack of significant behavioural differences between patients and control may be the result of the inclusion of patients with lower levels of depression in the analysis. Regional metabolic differences associated with performance on this measure may be attributable to a dysfunction of sustained attention that is related to the severity of depression.

In summary, functional neuroimaging studies of major depression for the most part appear to support the notion of a profile of cognitive dysfunction similar to that seen in the studies of cognition only. There is also considerable evidence to suggest that to some extent individuals with major depression are significantly impaired on a range of cognitive tasks, which may be the manifestation of a dysfunction in the central executive component of working memory. Furthermore, evidence from both structural and functional neuroimaging studies of MDD is indicative of abnormalities in the fronto-striatal system. Certainly, there is a striking pattern of prefrontal dysfunction associated with MDD, even in those studies that failed to find significant behavioural differences between depressed patients and

matched healthy controls. Indeed, such dysfunctions may underlie deficits in the allocation of processing resources. However, in order to qualify this assertion we need to examine current thinking regarding models of working memory and the pattern of cortical function that supports normal working memory. This shall be the focus of the following section of this review.

1.2 Working Memory

1.2.1 The structure of human memory

The basic requirements of the system human memory are the encoding, storage, and retrieval of information. It has been proposed that in order to perform these functions effectively the human memory system must consist of a sensory register, a short-term store, and a long-term store (see Figure 1.3).

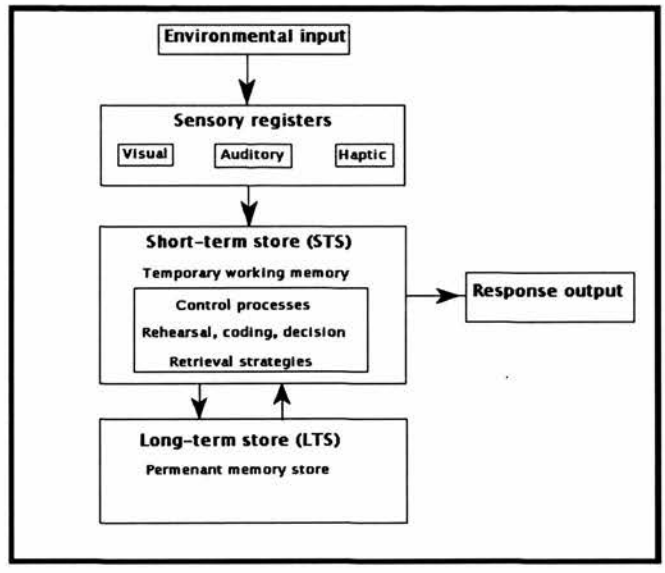

Figure 1.3: Schematic representation of the model of human memory as proposed by Atkinson and Shiffrin (1968; adapted from Baddeley, 1995).

The standard theory of human information processing (i.e. Atkinson & Shiffrin, 1968) states that information from the sensory modalities is received and temporarily stored in the sensory register. Information that is attended to is then transferred to the short-term store, where it is temporarily maintained prior to appropriate response, information loss, or transfer to the more permanent long-term store. Information is encoded into long-term memory by means of rehearsal, such as maintenance or elaborative rehearsal. Output from this system is mediated by the short-term store. Therefore, there must be a reciprocal transfer of information between short-term and long-term memory. Although this model of memory has proven extremely popular, certain shortcomings regarding the description of short-term memory in such a system have been suggested.

There have been numerous models of short-term memory that are consistent with the Atkinson and Shiffrin model of memory, and which inevitably share certain characteristics.

Such models of STM propose a system of limited storage and processing capacity, in which verbal memory span is heavily reliant on the capacity of STM. Moreover, traditional explanations of short-term memory imply a relatively passive form of information storage. However, it is apparent that this type of STS would not be capable of performing the variety of cognitive tasks that are evident in the observation of everyday information processing in humans. Indeed, it has been noted that the degree of interference experienced during dual task performance paradigms, compared to the performance of individual tasks, is not as acute as would be predicted by the original model of STM (Baddeley, 1999). Therefore, Baddeley proposed that the demands placed upon a short-term storage system required a more dynamic type of processing, such that a number of separate pieces of information could be held online at any one time and could be interrelated with information from both the STS and the LTS (Baddeley & Hitch, 1974). He described this type of short-term memory as 'working memory'.

1.2.2 Baddeley & Hitch model of working memory

As opposed to the passive 'buffer' storage system characterised by models of 'short-term memory', accounts of working memory attempt to characterise the more active nature of the human information processing (Newell, 1973). 'Working memory' refers to a cognitive system that provides temporary storage and manipulation of the information necessary to undertake complex cognitive tasks (Baddeley, 1992). Baddeley and Hitch (1974) proposed a model of working memory system that is characterised by an attentional control system, i.e. the 'central executive', which is subserved by two 'slave systems', i.e. the visuospatial sketchpad and the phonological loop (see Figure 1.4).

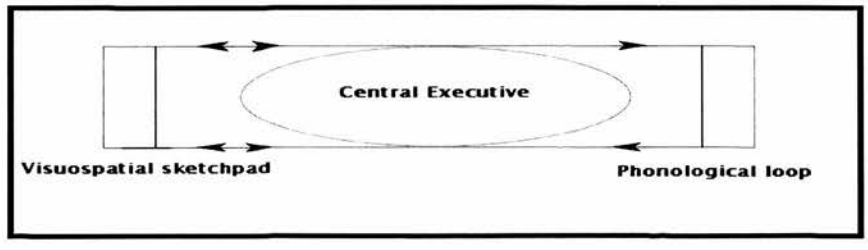

Figure 1.4: Schematic representation of the Baddeley & Hitch (1974) model of working memory.

The central executive is proposed to be a limited-capacity attentional system, which controls information transfer to and from the visuospatial sketchpad and phonological loop.

Moreover, it has responsibility for the association of these slave systems with the long-term memory store. Resultantly, the central executive is the most complicated aspect of the working memory system, and as such is probably the least understood (Baddeley, 1999). However, there is evidence to suggest that the capacity of the central executive, as assessed using measures of working memory span, is significantly correlated with an individual's comprehension capacity and with traditional measures of general intelligence.

The phonological loop, on the other hand, is involved in the processing of verbal information and, therefore, is comprised of a temporary store and a process for the rehearsal of verbal information. There is experimental evidence to support this notion of the role of the phonological loop. For example, a temporary store for verbal information is evidenced by the 'acoustic similarity effect' and the disruptive effect of task irrelevant spoken material on the recall of visually presented stimulus items. The acoustic similarity effect refers to the tendency for participant's errors to be phonologically similar to the correct stimulus item and for sequences of acoustically similar stimuli to be more difficult to recall in the same order than dissimilar items (Baddeley 1966: cited in Baddeley, 1999). Whereas, the latter effect has been noted in instances of the presentation of spoken material in both native and non-native language, but not using meaningless noise. Therefore, suggesting that the effect is related to sound rather than meaning, but is not just the result of distraction (Salame & Baddeley, 1982).

In addition, support for the presence of a phonological rehearsal process comes from experimental evidence of the 'word length effect'. It has been noted that in word recall tasks the greater the length of the words to be remembered the lower the average number of words recalled by participants (Baddeley, Thomson & Buchanan, 1975). If participants are prevented from engaging in subvocal rehearsal of the words, e.g. using articulatory suppression, then this effect disappears. Thus, indicating that this type of rehearsal process is an essential component of the temporary storage of verbal material.

It has been postulated that the visuospatial sketchpad is involved in the manipulation and maintenance of visual information. Evidence for these distinctions in the visuospatial sketchpad has come from studies of 'mental rotation'. In such tasks participants are presented with two visual stimulus items that have different orientations, and are asked to

decide whether the image are depictions of the same stimulus item. It has been suggested that participants complete this task by creating a visual image of the original stimulus item and mentally rotating this image to the match the orientation of the second item, and then making a decision regarding stimulus similarity. Indeed, the available evidence suggests that the time taken to make this decision is positively correlated with the extent of rotation in real space. Consequently, this sort of information processing must be reliant on the temporary storage and active manipulation of visual stimulus items, which corresponds to the account of visuospatial function in the Baddeley and Hitch model of WM.

Although there is abundant experimental support for the Baddeley and Hitch model of working memory, it has been noted that the original model could not fully account for the functions of an appropriate short-term store. Therefore, Baddeley proposed that a forth component be included in the model, i.e. an episodic buffer (Baddeley, 2000: see Figure 1.5). He suggested that the episodic buffer was a limited capacity storage system, which was capable of bringing together information from the other subsidiary systems and the long-term store, in order to provide a unitary episodic representation in short-term memory.

The Baddeley and Hitch model of working memory function has proven to be very popular, and the distinctions it makes appear to be supported by the behavioural evidence from normal adult participants. However, it is also important to determine whether the distinctions made in this model between the various cognitive components of the working memory system are reflected in the underlying biological systems. Indeed, studies of working memory impairments associated with specific hereditary disorders, such as William's and Down's syndromes, are indicative of a functional separability of the processing of visual and verbal information in the short-term (e.g. Jarrold, Baddeley & Hewes, 1999 and Wang & Bellugi, 1994). Both of these studies found evidence of significantly better verbal processing in William's syndrome patients, compared to Down's syndrome. Conversely, participant's with Down's syndrome performed significantly better on visuospatial short-term tasks. It was proposed that William's syndrome was associated with a specific dysfunction in the visuospatial sketchpad. Whereas, Down's syndrome individuals had an apparent deficit in the phonological loop, with relative sparing of visuospatial functions. Thus, these studies both observed pattern of results that support the idea of separate verbal and visual short-term memory stores.

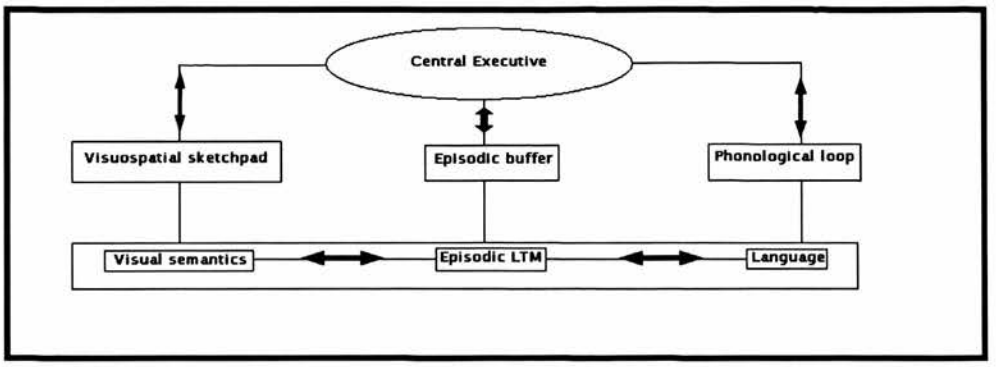

Figure 1.5: Schematic representation of the revised model of human working memory (adapted from Baddeley, 2000).

Although genetic studies do support the propositions of the above model of working memory, regarding the functional separability of the verbal and spatial short-term memory they do not elucidate as to the underlying mechanisms of the subcomponents of this system. However, examination of functional neuroimaging studies of working memory in healthy populations has not only revealed evidence relating to the separability of mechanisms of verbal and spatial short-term stores, but has allowed for investigation of the regions of cortical activation relating to the individual components of the working memory system.

1.2.3 Neuroimaging studies of working memory

There are numerous approaches to paradigm design in functional neuroimaging, including 'subtraction', 'parametric', 'factorial', and 'conjunction' approaches (see Chapter 2 for further details). However, studies of cortical activation associated with the performance of working memory tasks have largely utilised subtraction or parametric variations of three main types of working memory task: delayed response; n-back; and self-ordered tasks. The nature of working memory can be clarified by considering the contributions of each of these different approaches to the understanding of working memory function in normal populations.

(Note: A summary of those original articles considered for this section can be seen in Appendix 1E).

1.2.3.1 Subtraction studies of functional activation associated with working memory

Smith & Jonides examined the neural correlates of verbal, spatial, and object memory in a series of PET studies that used subtraction paradigms (i.e. Jonides et al., 1993; Smith & Jonides, 1994; Awh et al., 1996). The same basic DMTS paradigm was used in each of these

experiments to investigate the proposed distinctions in the working memory system. In the experimental condition of each study participants were asked to recall whether a probe-recognition item has previously appeared in a set of target items, i.e. either verbal (letters), spatial (dots) or object. Both global and regional blood flow under these conditions were compared to the pattern of cortical metabolism under a control condition, in which the target and probe information were presented simultaneously.

At a global level, the authors noted that all of the significant regions of activation in the spatial working memory conditions were in the right hemisphere (RH). On the other hand, performance of the verbal task was associated with activation in the left hemisphere (LH). Thus, global analysis implied a double dissociation in brain metabolism associated with performance of verbal and spatial working memory tasks. In order to expand upon these results, the experimenters examined regional changes in blood flow associated with the performance of each type of task.

The spatial task was found to be associated with activation in the right posterior parietal and anterior occipital cortices. Both of these areas have previously been identified as being involved in spatial processing/memory and the maintenance of visual images, respectively (Smith & Jonides, 1997). Moreover, spatial WM was also associated with activation in two frontal regions in the left hemisphere. However, the role of these regions was less clear. The authors suggested that this activation might have been involved a rehearsal process, similar to the subvocal rehearsal of information in the phonological loop.

Analysis of the regional changes in blood flow during performance of the verbal task revealed four LH regions of significant change, i.e. two frontal regions that included Broca's area, supplementary motor and premotor areas, and two regions in the posterior parietal cortex. The frontal activations occurred in regions that have previously been shown to be involved in higher-level speech processes (Fuster 1995; cited in Smith & Jonides, 1997). Therefore, it was suggested these regions might be involved in the subvocal rehearsal of verbal information. Posterior parietal cortex, on the other hand, has been suggested to play a role in the storage of verbal material. Patients with damage to this area have been noted to experience deficits in memory span for verbal material (Shallice 1988; cited in Smith & Jonides, 1997). Thus, this region is a possible location for the phonological store.

Between conditions comparisons were also conducted in order to determine the differences in activation between object and spatial conditions, and between object and verbal conditions. There was evidence of a double dissociation between global activation associated with object task performance and activation for spatial tasks, i.e. global analysis revealed that the majority of regions (i.e. 3 of 4) during performance of the object task were in the left hemisphere. The regional analysis demonstrated that the object task had resulted in activation in the same premotor and posterior parietal regions that were activated by the verbal task. A unique activation was also seen in the inferotemporal cortex – an area that is believed to be involved in object recognition. It was proposed that the activation seen in the left posterior parietal cortex might have been associated with participants creating a verbal description of the objects for the purpose of item rehearsal. Despite the similarities between the object and verbal conditions there was still dissociation in the global activation between these two task types. More specifically, inferotemporal activation was specific to the object task and some of the frontal activations were unique to verbal conditions.

Based on these observations, Smith and Jonides proposed that there was evidence of functional separability of the components of human working memory. Taking this into account, in a review of their neuroimaging studies of working memory they suggested an amended model of working memory, and included details of the regions they believed were integral to the normal functioning of this type of short-term memory system (see Figure 1.6; Smith & Jonides, 1997).

There are also other investigations which support the notion of a spatial dissociation in regions of significant change in brain metabolism associated with different subtypes of working memory. D'Esposito and colleagues conducted a review of functional neuroimaging studies of spatial and nonspatial (i.e. verbal and object) working memory. The authors considered evidence of significant signal change from twenty different neuroimaging studies. Examination of locations of lateral prefrontal activation revealed that the activation associated with the performance of both spatial and nonspatial tasks was evenly distributed throughout the lateral PFC, i.e. there was no dorsal/ventral dissociation between different task types. However, there was evidence of hemispheric specialisation associated with working memory function. Spatial tasks were associated with greater

activation in the right PFC, whereas nonspatial tasks generated greater left hemisphere activation in PFC (D'Esposito et al., 1998).

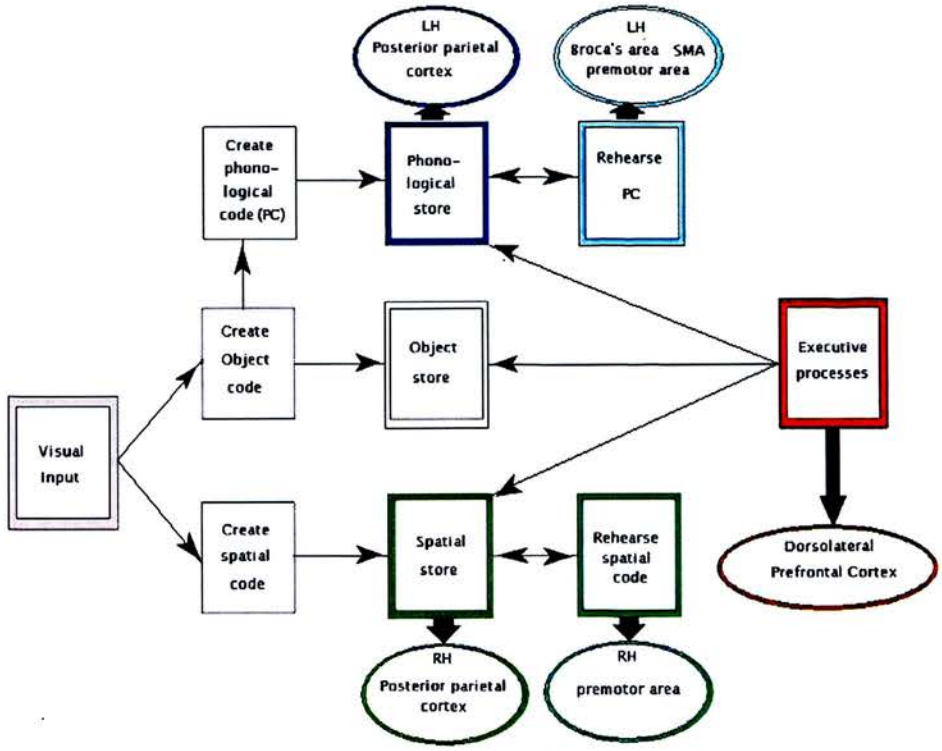

Figure 1.6: Graphic representation of Smith & Jonides' proposed model of cortical regions supporting working memory function (adapted from Smith & Jonides, 1999). This schematic representation of the processes involved in working memory and the regions of cortical activation resulting from the presentation of stimulus information in the visual modality. Note: Block arrows indicate region(s) of associated activation for specific components of the WM system.

Paulesu, Frith, and Frackowiak (1993) also investigated the spatial dissociation of the regional activations associated with different working memory processes with respect to verbal working memory. Participants in this study were asked to undertake two different tasks: short-term memory for letters and rhyming judgement for letters. It was proposed that the former task would only engage the short-term store, whereas the latter would be reliant on the subvocal rehearsal system. Therefore, the authors suggested that by measuring the relative activity generated by each of these tasks it should be possible to determine the cortical areas supporting each of these processes. Analysis of PET acquired imaging data revealed that phonological processing was associated with significant

activation bilaterally in BA 44, superior temporal gyri (BA 22/42), supramarginal gyri (BA 40) and insulae. The authors suggested that this arrangement of regions comprises the functional anatomy of the phonological loop. Moreover, an attempt to identify those regions associated with specific phonological functions implied that the supramarginal gyrus (BA 40) was the primary location for the phonological store, and that Broca's area (LH; BA 44) was essential for subvocal rehearsal. Significant activations were also noted in the supplementary motor area (SMA) and cerebellum, and possibly the sensory-motor areas. However, it is possible that these additional activations were related to the activation of a network associated with language planning and execution (Paulesu, Frith & Frackowiak, 1993).

In addition to the highlighted frontal and parietal activations, working memory function has also been linked to activation in the anterior cingulate, occipital cortex, and the cerebellum (Cabeza & Nyberg, 2000). Indeed, changes in the degree of activation in the anterior cingulate (BA 32) have regularly been noted in studies of working memory. However, there is evidence to suggest that such activations may not reflect specific working memory processes, but instead may reflect the degree of difficulty of the task. Barch and colleagues studied the performance of neurologically normal participants on the continuous performance test (CPT; Rosvold et al., 1956). Demand on working memory was varied on this task by varying the delay time between the cue and the probe on this task, whereas presenting either degraded or non-degraded stimulus items altered task difficulty. Regions that showed an effect of delay on activation included the left middle frontal gyrus (corresponding to DLFPC, the left inferior frontal gyrus (BA 44), and the left posterior parietal lobule. None of these regions showed an activation response to the changes in task difficulty. However, a number of regions did show a response in activation as a result of manipulation of task difficulty, including the anterior cingulate, right inferior frontal cortex, and a subcortical region. The effect seen in these regions was greatest in the anterior cingulate (Barch et al., 1997). Thus, supporting the proposed role of AC activation in the mediation of responses to the manipulation of task difficulty.

Therefore, it appears that there is a hemispheric dissociation in cortical activation during performance of different types of working memory task: spatial/left hemisphere and nonspatial/right hemisphere. There is also evidence to suggest that specific regions, or

assemblies of regions, support specific processes in the working memory system. Moreover, there appears to be dissociation between those regions of cortex that are associated with the level of difficulty of certain working memory tasks and those which are associated with the processes of working memory. However, an additional factor yet to be considered is the effect of cognitive load on the working memory system.

1.2.3.2 Parametric investigations of functional activation associated with working memory

A number of the studies already mentioned have relied on subtraction paradigms in order to make inferences about the functional neuroanatomy of human working memory. While such investigations have inevitably been useful in developing our understanding of working memory and its underlying processes there are complications that are intrinsic to this type of approach. The most obvious of which is the problem of 'pure insertion' (see Sternberg, 1969). In such paradigms the determination of the pattern of activation associated with a specific process is reliant on the assumption that the two chosen tasks (i.e. the experimental task and the control task) differ only in the inclusion of the process of interest, and that inclusion of this process does not impact upon other aspect of information processing. However, it is reasonable to assume that the inclusion of the process of interest may have a noticeable effect on the execution of other processes necessary for the successful completion of a given task. Moreover, it may rely on the implication of supplementary processes not required the control task.

One potential way to address this issue is to instead employ a single behavioural measure that can be varied around a single parameter, i.e. parametric paradigms. The use of parametric measures allows the experimenter to keep all other cognitive factors constant while incrementally increasing (or decreasing) the level of difficulty of the process of interest. This approach has been of particular use in the functional neuroimaging studies of working memory as it has enabled investigators to determine not only those regions that may be associated with the verbal or spatial aspects of WM but to ascertain cortical regions that correspond to central executive function, i.e. those regions which respond to alterations in cognitive load.

Many investigators have employed variations on a parametric working memory task known as the 'n-back' task in order to investigate both verbal (e.g. Cohen et al., 1994; Schumacher et

al., 1996; Braver et al., 1997; Cohen et al., 1997; Manoach et al., 1997; D'Esposito et al., 1998; Ye et al., 1998; Isoardi et al., 1999; LaBar et al., 1999; Rypma et al., 1999; Honey, Bullmore & Sharma, 2000; Nystrom et al., 2000; Glabus et al., 2003) and spatial (e.g. Casey et al., 1998; D'Esposito et al., 1998; Callicott et al., 1999; Thomas et al., 1999; Jansma et al., 2000; Nystrom et al., 2000; Postle et al., 2000) working memory systems. This paradigm has been developed from a task that was originally used in an EEG investigation of the spatiotemporal dynamics of human working memory (i.e. Gevins & Cutillo, 1993). Normally the task is presented as a delayed match-to-sample task, in which participants are presented with a series of visual arrays (either spatial or nonspatial). The level of difficulty of the n-back task is then manipulated by altering the number of intervening arrays between presentation of the items to be recalled and the probe for recall of the items. Commonly, difficulty is varied around four levels of this parameter, i.e. 0-, 1-, 2-, and 3-back. In 0-back conditions participants simply have to respond to the current stimulus items. However, in 1-back conditions they are required to respond to the items that appeared in the previous array. Similarly, in 2- and 3-back conditions there are 2 and 3 intervening stimulus arrays between encoding and response, respectively.

Performance on the n-back task can be measured on two factors, i.e. accuracy and reaction time. It has been observed that as the level of task difficulty is increased (i.e. from 0-to 3-back) there is a corresponding decline in participant's accuracy, and an increase in reaction time (e.g. Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000). Indeed, reaction time has been highlighted as a measure that is sensitive to manipulations of memory load (Baddeley, 1986). Therefore, it can be predicted that the changes in cortical activation that accompany the increase in n-back, and thus the increase in memory load, will be associated with a decline in the performance of participants.

The n-back task has proven popular with researchers examining the functional anatomy of working memory for a number of reasons. Primarily, variations on the task have produced robust findings regarding the functional underpinnings of WM (e.g. Casey et al., 1998). Moreover, it is reasonably easy to manipulate the task around a number of factors while still retaining the essential components that contribute to its reliability. Experimenters have designed both verbal and spatial variants and the paradigm can be altered to assess either recognition or recall ability. Moreover, the level of difficulty of the task can be easily altered

in order to bring about changes in cognitive load. The ease with which this task can be adapted for the needs of a single study, or series of studies, makes it particularly amenable to the understanding of the processes of working memory not only in normal participants but also in clinical populations.

Verbal working memory

Neuroimaging studies that have used variants of the n-back task to investigate working memory have largely concerned themselves with the neural correlates of the increase in task difficulty (see Figure 1.7). Braver and colleagues conducted two fMRI investigations of verbal WM across 0- to 3-back levels of n-back (Braver et al., 1997). The variations of the task that they employed in the two studies were essentially the same, although the paradigm used in the second study comprised shorter block durations and included fewer trials of each level of the task. In their first study they noted a linear change in the degree of activation in the middle frontal gyrus (MFG; BA 46/9) bilaterally, the left inferior frontal gyrus (LIFG; BA 44/45), the anterior cingulate (BA 32), and a more anterior inferior site (BA 47/10). However, planned comparisons revealed monotonic changes in activation associated with increased task difficulty in MFG and LIFG only. In both instances there was a linear relationship between signal and load. Moreover, they noted similar findings in their analysis of the relationship between RT and signal change.

The results of the second study by this group for the most part replicated the findings of the first. However, in this instance load-sensitive activity was additionally observed in the right homologue of LIFG (BA 44), left frontal operculum, and a number of motor, premotor, and supplementary motor regions (BA 4 & 6). Additionally, non-frontal activity was noted in bilateral posterior parietal cortex (BA 40/7) and the left caudate nucleus.

The load-dependent activity of these cortical regions has been observed in other studies that have also employed verbal variations of the n-back task. For example, in an fMRI investigation of the effects of both time and load on activation, Cohen and colleagues also noted a significant effect of memory load in DLPFC (Cohen et al., 1997). Moreover, areas of posterior parietal cortex (BA 40) and in posterior regions of frontal cortex (including Broca's area) were also found to be sensitive to the effects of load, but also co-occurred with regions that were sensitive to the effects of time and load. This study also noted significant effects of

time, but not load, in visual, motor, and somatosensory cortex. While the pattern of results in this study is similar to that seen in the Braver study, the effect of load on PFC in this case appeared as a step function rather than a monotonic linear increase across all levels of the task, i.e. the primary increase in activation occurred between the 1- and 2-back levels of the task.

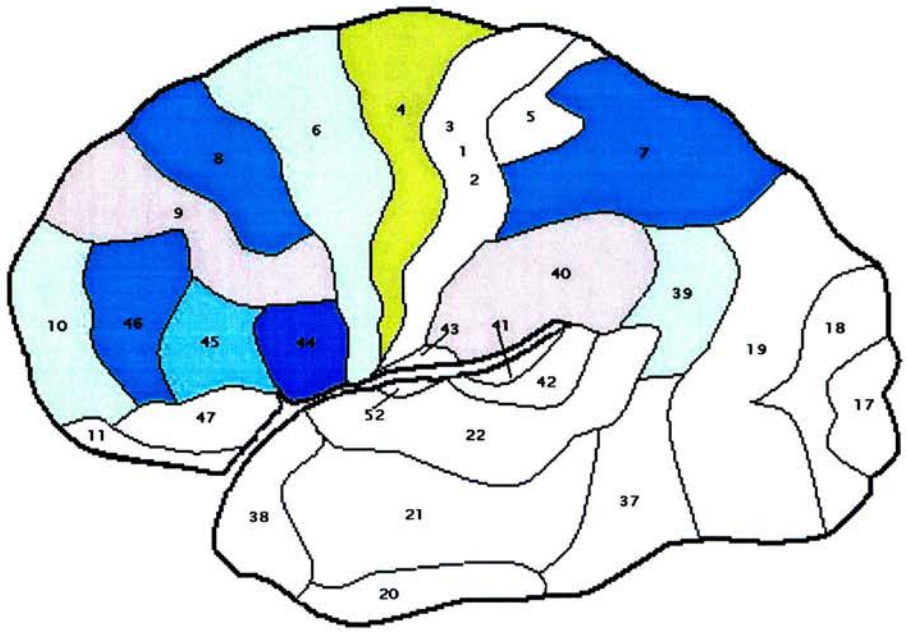

Figure 1.7: Diagram of regions of cortex exhibiting load dependent activity during performance of parametric working memory tasks – lateral view. The numbers on each cortical section correspond to Brodmann areas. Note: The choice of colour of each of the relevant sections is unimportant. A range of colours has been used in order to highlight the structural distinction between the various regions involved in load-dependent activity.

The relative effects of time and load on the pattern of cortical activation were also noted in a PET investigation of verbal n-back performance, conducted by Smith and Jonides (i.e. Jonides et al., 1997). This study observed a pattern of results that indicated that as the level of difficulty of n-back was increased there was an apparent increase in the number of activated regions, including DLPFC. However, further analysis revealed that the same regions were active across all levels of the task (i.e. 0- to 3-back), but that at lower levels of the task the signal intensity in the activated regions was below threshold. Linear increases in activation with increasing memory load were noted in the bilateral cerebellum, bilateral DLPFC (LH: BA 46/10, RH: 9/10/46), Broca's area, right superior parietal cortex (BA 7), right premotor cortex (BA 6), and a region comprising the left premotor area and the anterior

cingulate (BA 6/32). As in the Cohen study, activation in the visual, motor and somatosensory cortex was significant but not associated with memory load per se.

Thus, the available evidence indicates that the regions of cortical activation associated with verbal working memory processes in subtraction studies also exhibit significant changes in signal intensity under parametric paradigm conditions. Moreover, regions within the proposed cortical assembly supporting verbal WM show monotonic, or at least linear, changes in activations with relative increases in memory load. A similar pattern of results has also been noted in parametric studies of regional activations associated with spatial working memory.

Spatial working memory

In an parametric study of spatial working memory, Callicott and colleagues noted load-sensitive responses in a distributed network of regions that included DLFPC (BA 9-10/44-46), premotor cortex (BA 6/8), the basal ganglia and thalamus, parietal cortex (BA 7/39-40), and in a pericingulate regions comprising the medial frontal gyrus (BA 6) and the anterior cingulate (BA 32). Moreover, there was evidence of significant laterality in the regions of activation associated with memory load. The number of significant foci of activation in DLPFC was greater in the right hemisphere, compared to the left, and included both dorsal (BA 9/46) and ventral (BA 6/8 areas). Interestingly, the authors also observed that the signal change in DLPFC loci evinced a U-shaped response to the linear increase in task difficulty. It was suggested that this pattern of activation was evidence of a capacity-constrained response. This proposal was additionally supported by the observed predictive value of DLPFC activation and performance within capacity (i.e. 2-back condition), but to a much lesser degree beyond capacity (i.e. 3-back) (Callicott et al., 1999).

As with activation associated with verbal WM, prefrontal load-dependent activation during performance of spatial n-back tasks has also been observed in other functional neuroimaging studies of WM in normal adults (e.g. Casey et al., 1998; Jansma et al., 2000; Postle et al., 2000). Moreover, there is evidence to suggest that the co-localisation of load-sensitive and load-insensitive activations is also apparent in spatial WM tasks. Jansma examined spatial working memory across four levels of n-back, and found evidence of co-localisation of these

two response types bilaterally in DLPFC and parietal cortex, and in the anterior cingulate (Jansma et al., 2000).

This model of activation associated with parametric spatial WM performance can also be extended to populations other than normal healthy adults. Thomas and colleagues found evidence of activation of similar cortical regions in healthy adults and children (aged 8 –10 years) in an fMRI investigation of spatial WM. In a comparison of adults and children on the n-back task and a control motor condition revealed that both experimental groups experienced reliable working memory associated activation in the right hemisphere in the superior frontal gyrus (BA 8), DLPFC (BA 10/46), superior parietal cortex and bilaterally in inferior parietal cortex. Thus, indicating that the same regions of cortex subserves working memory in both children and adults (Thomas et al., 1999).

In addition to the investigation of the regions of activation associated with performance of working memory tasks have highlighted significant factors the impact upon the observed cortical function. In a recent fMRI investigation of verbal working memory, using the n-back task, Glabus highlighted significant differences in the regions of activation associated with task performance between sub-groups of 'high' and 'low' performers. Although the group model of activation in this study highlighted regions of significant activation in the prefrontal and parietal cortices, there were considerable interindividual differences in activation. It was found that those who performed well on the task (i.e. high performers) engaged a LH sub-network, which comprised the inferior parietal lobule and Broca's area, whereas, those participants who were relatively impaired on the paradigm (i.e. low performers) utilised a RH sub-network including inferior parietal and DLPFC. Therefore, the authors suggested that better performance on measures of verbal WM is associated with activation of neural systems associated with verbal information processing. Moreover, it was proposed that an observed interaction between the parahippocampal gyrus and the inferior parietal lobule may have been associated with the implementation of different task strategies (Glabus et al., 2003).

There is also evidence to imply the same kind of performance related activation associated with measures of spatial working memory. Although they did not directly compare different sub-groups of participants, Jansma and colleagues did note a significant positive

correlation between performance (i.e. accuracy) and activation in a large region of load-sensitive activity in the anterior cingulate and in a smaller region of load-sensitive activity in the right parietal cortex. However, given the previously outlined response of anterior cingulate to aspects of task difficulty, this may simply reflect the increased level of task difficulty rather than a functional dissociation associated with the level of performance of individual participants.

In summary, it appears that the proposed dissociation between verbal and spatial working memory functions is reflected in the hemispheric specialisation associated with each separate form of WM (i.e. spatial WM → RH, and verbal/nonspatial → LH). There is also evidence to suggest that activation in specific cortical regions is associated with the performance of specific processes within each of the working memory slave systems, such as storage and rehearsal, with prefrontal regions apparently supporting spatial and verbal rehearsal and parietal regions functioning in the short-term storage of spatial and nonspatial material. Moreover, evidence from parametric working memory tasks is indicative of load-dependent activity in a distributed network of prefrontal and posterior parietal regions associated with executive, storage, and rehearsal functions of WM. Specifically, it has been suggested that, as a result of its sensitivity to changes in memory load, the DLPFC may be the functional site of the central executive component of human working memory. Although, there is evidence of activation in visual, motor, and sensorimotor areas associated with the performance of working memory tasks such activation is not load sensitive and may reflect motor aspects of working memory, such as speech planning and execution.

1.3 Antidepressant medication and cognition

1.3.1 Pharmacotherapy and depression

1.3.1.1 The monoamine hypothesis of major depression

The monoamine (or biogenic amine) hypothesis of major depression postulates that MDD is the result of abnormalities in neurotransmitter function in the brain. More specifically, it proposes that depressed mood is the consequence of deficiencies in monoamine neurotransmitters, such as noradrenaline (NA) and serotonin (5-HT).

Evidence for this hypothesis was first suggested by the observation that manipulations of the levels of biogenic amines could either induce or alleviate the symptoms of major depression. For example, an investigation in the mid-fifties found that consumption of the antihyperintensive medication resperine precipitated depressed mood (i.e. Muller et al., 1955; cited in Hirschfeld, 2000). It was found that resperine interfered with the storage of 5-HT in two ways, i.e. through the depletion of stores of serotonin in the brain and the storage of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in urine (Shore, Silver, and Brodie, 1955; cited in Hirschfeld, 2000). Therefore, it has been proposed that resperine brings about depletion in the presynaptic level of monoamines, as a result of its disruption of the vesicular storage of both NA and 5-HT, and that this depletion is critical in the noted induction of depression associated with resperine administration.

The notion of the role of monoamines in the precipitation of depression is also supported by the observed reversibility of depressive symptoms upon cessation of resperine. Moreover, a normalisation of mood can be attained via the administration of monoamine precursors, such as dihydroxyphenylalanine, which effectively reverses the impact on monoamine levels caused by medications such as resperine. The result of which is a normalisation of mood. This effect has been noted in both animal models and human participants.

The role of 5-HT and NA in depression has been further supported by observation that medications used in treatment of depression appear to remedy the depressive symptoms by altering the synaptic availability of monoamines. For example, the action of both the tricyclic and monoamine oxidase inhibitors (MAOIs) in alleviating depressive episodes appears to be the result of their ability to increase the level of monoamines at the synapse.

However, the relationship between mood and monoamine levels may not be as simple as this theory predicts. In studies of normal healthy participants depletion of 5-HT and NA, i.e. via tryptophan depletion or administration of low doses of α-methyl-*p*-tyrosine, has not necessarily led to the onset of depressive symptoms. Moreover, depressed patients who are treated with either 5-HT selective reuptake inhibitors, but not NA reuptake inhibitors, may suffer a brief relapse upon depletion of 5-HT. Conversely, those patients who are treated with NA reuptake inhibitors, but not 5HT-reuptake inhibitors, can experience relapse if briefly exposed to depletion of NA. However, the experimental evidence suggests that although their depletion is not sufficient alone to induce depression, monoamines may be critically involved in the maintenance of antidepressant response (Duman, 1999).

While there is a clear association between monoamine availability and depression, there are also a number of problems with this hypothesis, such as the delayed action of many antidepressants. Although many antidepressants will have an impact upon monoamine levels within hours of the first administration it can sometimes be weeks before an effect upon mood will be noted in the depressed patient. Thus, suggesting that while the alteration of the level of monoamines at the synapse is necessary, it may not be sufficient alone in the reversal of depressive symptoms. Nonetheless, despite such criticisms the monoamine hypothesis of depression has remained one of the most influential, and has largely dictated the psychopharmacological approach to the treatment of major depression.

1.3.1.2 Classes of antidepressant medication

It has been proposed that the mechanisms that lead to the transportation of biogenic amines such as 5-HT, NA, and dopamine (DA) to the presynaptic cortical neuron are essential to the termination of the physiological actions of these transmitters on their receptor sites. Consequently, any action that inhibits this re-uptake mechanism should both prolong the physiological action of the neurotransmitter and bring about relevant behavioural changes (Leonard, 1992). However, this action alone does not appear to be sufficient to bring about changes in depressed mood. For example, drugs such as cocaine and amphetamine, which bring about delay in the re-uptake of biogenic amines, appear to have little effect on depression. Even so, the pharmacological treatment of major depression has largely focussed on those treatments that have an effect on the re-uptake of monoamines.

Despite similarities in their physiological actions, antidepressant medications can bee categorised into different subtypes. The classification of antidepressants is largely based upon the known receptor affinities of antidepressant medications. The result of adopting this approach to the classification of medications used in the treatment of depression is three general classes of antidepressant (AD) medication, i.e. the previously mentioned tricyclic antidepressants (TCAs) and MAOIs, as well as the more modern selective serotonin re-uptake inhibitors (SSRIs). Although there are similarities in the mechanisms of each of these classes of AD, there are crucial differences in the antidepressant action of each different subtype. Therefore, it seems appropriate to examine the nature of each class independently.

Tricyclic antidepressants

Tricyclic antidepressants get their name from the presence of a core structure comprised of three benzene rings. Included in this class of medications such as imipramine, amitriptyline, trimipramine, doxepine, desipramine, nortriptyline, and protriptyline. The primary action of TCA drugs is in the inhibition of the re-uptake of NA, and, to a lesser degree, 5-HT.

In addition to their affinity for biogenic amine receptors, TCAs are also active at multiple nonmonoamine sites, such as histamine-1, muscarinic acetylcholine, and α_1-adrenergic receptors. Many of the side effects associated with TCA medications can be attributed to the affinity for these drugs at these nonmonoamine receptor sites, at therapeutic dose levels. Indeed, this varied affinity has been implicated in a number of the potential side effects associated with therapeutic usage of TCAs, including dry mouth, blurred vision, constipation, urinary retention, memory impairment, tachycardia, sedation, weight gain, hypotension, and potentiation of other CNS depressants (Berman et al., 1999). Due to the risk and range of side effects associated with tricyclic medications, other classes of antidepressant medication are more commonly favoured over TCAs in the treatment of MDD.

Monoamine oxidase inhibitors

Medications within the MAOI class, such as phenelzine, tranylcypromine, and moclobemide, are categorised by their ability to block the action of the MAO isozymes A and B. The antidepressant activity of this class of drugs is largely attributed to their ability to block MAO_A, since the inhibition of MAO_B has limited effect on the symptoms of major

depression. The result of this action is a decrease in the metabolism of NA, thus increasing the synaptic availability of this monoamine.

The side effects of MAOIs have been known to include acute and severe elevations of blood pressure, headaches, nausea, sweating, pallor, and vomiting. Moreover, patients taking MAOIs may have to adhere to strict dietary restrictions. Resultantly, MAOI antidepressants are relatively less popular in the treatment of MDD than other AD medications.

Selective serotonin reuptake inhibitors

As with the TCA medications, SSRI antidepressant act upon the uptake of both NA and 5-HT. However, their affinity for the 5-HT transporter is in order of 1-2 times the magnitude of their affinity for NA (Richelson, 1991; cited in Berman et al., 1999). Given their relative effectiveness and tolerability, SSRI medications such as fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram are in common use for the treatment of MDD.

Although there is a considerable range of studies that have examined the affinity, efficacy, and tolerability of the various classes of antidepressant medications, the relevance of AD medication to this particular series of investigations is their impact upon cognitive performance and cerebral metabolism. Therefore, the following sections of this review will consider the available evidence pertaining to each of these factors.

1.3.2 The profile of cognitive function associated with antidepressant medication

It is commonly accepted that the advent of adequate psychopharmacological treatments for depression has fundamentally changed the evolution and prognosis of MDD (Amado-Boccara et al., 1995). Moreover, it has been proposed that modern ADs make it possible individuals with major depression to be treated as outpatients and to retain much of their normal activity, including work responsibilities. However, for depressed patients to maintain a level of functioning that is as close as possible to normal it is essential that the antidepressants which patients are prescribed impact minimally upon cognitive function.

The association between cognitive performance and antidepressant medication is also a key factor in patient compliance. Indeed, it has been found that patients are less likely to comply with pharmacological intervention if they experience disturbances of mnemonic or

psychomotor function (Amado-Boccara et al., 1995). The profile of cognitive function associated with AD medication is not only of concern in a clinical setting. Indeed, the consumption of ADs is a potential confounding factor in empirical investigations of major depression. Therefore, it is essential that researchers and clinicians are able to identify and quantify possible dysfunctions of cognition that are associated with the administration AD medication, rather than being symptomatic of MDD.

A number of studies have investigated whether the consumption of AD medication has a significant association with cognitive performance, on a number of different cognitive measures. There has been considerable variation in the methodological approaches of different studies, including differences in the type of antidepressant investigated, the experimental groups of interest (i.e. normal healthy adults or depressed patients), the cognitive processes of interest, and the choice of AD administration (i.e. acute, subacute, or chronic). The consideration of a selection of original articles and review papers which have examined these factors should allow us to determine: (1) whether the consumption of antidepressant medication has a significant impact upon cognitive function, and (2) which factors in experimental design are pertinent to the observation of cognitive dysfunction in individuals who have been prescribed an AD.

Psychomotor function

Manipulation of the serotonergic system has been shown to have an impact upon many aspects of cognitive performance, including psychomotor function (reviewed by Lucki, 1998). Therefore, studies of the effect of antidepressant medication on cognition have tended to include measures of psychomotor ability. The measures used in the assessment of psychomotor function have ranged from elementary tests of motor ability, such as the finger tapping test (FTT), to more complex assessments which mimic real life situations, e.g. tests that simulate driving. The outcome of the investigation of measures of psychomotor ability appears to be reliant on the class of medication used and the affinity of the chosen medication.

A key factor in the effect of antidepressant medication on psychomotor performance appears to be the receptor affinity of the chosen AD. Acute administration medications that have a biochemical profile that includes affinities for muscarinic acetylcholine, H_1-histaminic, and

α_1-andrenergic receptors appear to have a deleterious effect upon measures of psychomotor performance, whereas those medications which are primarily involved in the inhibition of 5-HT uptake appear to have no such detrimental effect (reviewed by Amado-Boccara et al., 1995). Thus, there appears to be a proposed distinction between the effect of TCA and SSRI medications in the performance of measures of psychomotor function.

Indeed, a number of empirical investigations have noted the differential effect of TCA and SSRI medication on the measures of motor function. For example, Fairweather and colleagues conducted a comparison on the effect of citalopram (an SSRI) and dothiepin (a TCA) in a sample of healthy participants (i.e. N = 14; 5 male and 9 female participants). Participants were prescribed citalopram (i.e. 10, 20 or 40 mg/day for 8 days), dothiepin (75mg on days 1 & 8, with placebo on intervening days), or a placebo only (once daily for 8 days). Each participant was tested on a battery of neuropsychological assessments at 2-, 4-, 5-, and 8-hour intervals after consumption of medication on days 1 and 8 of the study, i.e. prior to commencement of medication, and after subacute administration of medication. It was found that while citalopram had no significant effect on psychomotor performance on both a choice reaction time and the Leeds Psychomotor Test, irrespective of dosage. Dothiepin, on the other hand, was found to induce a sedative effect on motor function on all of the measures which were used (Fairweather et al., 1997). These findings replicated those of an earlier study by the same research group, which found no effect of fluvoxamine (an SSRI) on the same measures of psychomotor performance in healthy male volunteers (i.e. N = 12), but the same sedative effect of dothiepin (Fairweather, Ashford & Hindmarch, 1996).

The comparative effects of TCA and SSRI medications on motor performance have also been extended to studies of more complex motor function. Hindmarch studied the impact of fluoxetine (an SSRI) and dothiepin on the performance of a simulated driving task. As with the previous investigations this study involved normal healthy adults, who acted as their own controls in a placebo-controlled study. Participants' performance on the driving simulation task was measured on a number of performance factors, and under two 'alcohol' conditions, i.e. consumption of medication either with alcohol or an alcohol placebo. Irrespective of the consumption of alcohol, dothiepin impaired performance on the task. However, acute dose administration of fluoxetine had no impact upon performance in both alcohol conditions (Hindmarch, 1988). Thus, indicating that the sedative effects of TCAs

upon psychomotor performance in normal healthy adults is not just applicable to elementary measures of motor function, but can indeed be extended to more complex forms of psychomotor ability.

One potential explanation of the relative differences in the effect of TCA and SSRI medications on the performance of psychomotor tasks may be attributable to the differences in the affinity of these two classes of AD medication to NA receptors. In order to determine the relative effect of 5-HT and NA reuptake inhibition upon cognitive performance, Nathan and colleagues examined the comparative effect of serotonin and noradrenaline reuptake inhibitors (i.e. citalopram and venlafaxine, respectively). The effect of both of these medications upon the performance of a choice reaction time measure in normal healthy volunteers (i.e. N = 9, all male) was compared to the effect of amitriptyline (a TCA) and a placebo. It was found that acute administration of citalopram actually had a facilitatory effect on psychomotor function, which was evident in decreased reaction times on the CRT task in participants in this condition. Alternatively, venlafaxine was found to have no effect on any measure of psychomotor speed in this study (Nathan et al., 2000).

The results of the Nathan study appear to support the notion of a lack a sedative effect of SSRI medication on psychomotor performance. Indeed, the findings of this particular investigation are indicative of an improvement in psychomotor function in participants who are given SSRI medication. This beneficial effect of 5-HT reuptake inhibition on psychomotor performance has also been noted in studies that have administered other SSRI medications, such as sertraline (Hindmarch & Bhatti, 1988) and paroxetine (Hindmarch & Harrison, 1988). Thus, it would appear that the effects of SSRI medication on psychomotor performance are at worst negligible, and may even beneficial.

The failure of venlafaxine to impact upon psychomotor function may be attributed to its low affinity for 5-HT receptors, compared to SSRI medication. Although venlafaxine does have some affinity for the re-uptake inhibition of 5-HT the magnitude of its effect on this mechanism is somewhere in the order of 160 times less than that of citalopram (Nathan et al., 2000).

The relative difference in the effect of venlafaxine and citalopram also has important consequences in the comparative differences between TCA and SSRI medications on motor function. Venlafaxine is similar to TCA medications in its profile of affinity for NA reuptake inhibition. Therefore, the sedative effects of tricyclics may possibly be attributable to the affinity of this class of medication for nonmonoamine receptor sites.

Executive function

Monoamine function in the brain is not only of importance to the integrity of psychomotor function, but also plays a role in carrying out executive functions. In a review of chemical modulation of executive functions in the brain, Robbins suggested that catecholamines (i.e. DA and NA) were involved in the execution of tests of planning or working memory, whereas serotonin function appears to be involved in set-shifting and decision-making tasks (Robbins, 2000). This behavioural dissociation is also reflected in the functional dissociation of the putative regions of PFC that support these types of executive function. It would appear that the effect of catecholamines on cognitive performance is associated with those tasks reliant on dorsolateral and rostrolateral PFC. Serotonin, on the other hand, seems to be involved in the execution of tasks that are mediated by orbitofrontal PFC (Robbins, 2000).

Therefore, given the relative effect of different biogenic amines on cognitive function, it is reasonable to suggest that medications that have an effect upon the cortical levels of these neurotransmitters will have an impact upon executive function. As with psychomotor function, a number of studies have considered the relative effects of such medications on different aspects of executive function, including planning, working memory, and selective attention. Moreover, some investigations have also considered the relative influence of different classes of AD medication on these types of cognitive functions.

One commonly used objective measure of attention and information processing in studies of antidepressant effects on cognition is the critical flicker fusion frequency threshold (CFFT). This assessment requires participants to respond at the frequency at which a rapidly repeated visual stimulus (i.e. light emitting diodes) stops being perceived as separate stimulus items and instead appears to be a continuous light. This measure has produced reliable evidence of information processing effects of ADs, and has also been suggested as an appropriate measure of central nervous system (CNS) function.

A review of studies that have used the CFFT to measure information processing ability in normal participants found that all studies meeting the inclusion criteria for the study observed a significant impairment of CFFT associated with the administration of TCAs (cited in Hindmarch, 1995). In contrast, SSRIs have been associated with an increase in CFFT. This latter effect has been noted with a variety of different SSRI medications, such as sertraline (Hindmarch & Bhatti, 1988), citalopram (Fairweather et al., 1997; Nathan et al., 2000), and paroxetine (Hindmarch and Kerr, 1994; cited in Hindmarch, 1995). Moreover, the positive effect of SSRIs on CFFT has been observed to be immediate and dose dependent. Therefore, the experimental evidence is suggestive of impairment in information processing and CNS function associated with TCA treatment. However, the administration of SSRIs seems to be associated with sparing or enhancement of these functions.

Selective attention has also been assessed in studies of the behavioural toxicity of antidepressants using measures such as the continuous performance test (CPT), the symbol cancellation test of the WMS-R, the Digit Symbol Substitution Test (DSST), and the Stroop colour-naming test. In single dose investigations of the effect of ADs on cognition in healthy adults impairments, on measures of selective attention have been noted with the administration of a range of TCA medications, such as amitriptyline and imipramine. However, these impairments have not been observed in studies of long-term repeated administration of TCAs in both healthy and depressed experimental groups. Indeed there is evidence to suggest that in the case of amitriptyline performance may return to baseline levels in chronic AD administration paradigms. This is again in contrast to the effect of SSRI medications, which appear to have either no sedative effect or a positive effect on measures of selective attention when administered acutely to healthy volunteers. This pattern of findings also seems to extend to the long-term administration of these drugs in both depressed patients and healthy controls (see Amado-Boccara et al., 1995 for review).

The relative effect of TCAs and SSRIs on other measures of executive function, such as working memory has also been considered. For example, van Laar and colleagues investigated the relative effects of a weeklong course of amitriptyline, nefazedone (i.e. a 5-HT2 receptor agonist), or paroxetine on a working memory task, in a sample of healthy volunteers (i.e. N = 24; 12 male and 12 female). The authors found that amitriptyline resulted in increased reaction times on the first day of testing (i.e. day 1), whereas paroxetine

and nefazedone were both associated with a decrease in RT. With the exception of nefazedone, the deviations from baseline were found to have largely diminished by the final day of testing (i.e. day 8). Performance on the working memory task in this study was also measured in terms of the percentage of misses and false alarms. At day 1, amitriptyline resulted in an increase in the percentage of misses, although the other medications had no effect at this point on this measure. However, by day 8 both paroxetine and nefazedone had resulted in a significant increase in the percentage of misses, and there was a trend towards a significant increase associated with amitriptyline. The only other significant finding in this study was a significant increase in the percentage of false alarms on day 1 in those participants taking the TCA (van Laar et al., 2002).

These observations are in concordance with the noted predictions of Robbins, which stated that the manipulation of the serotonergic system would be expected to have no effect on measures of working memory, whereas the manipulation of catecholamine systems may possibly lead to the disruption of working memory ability (i.e. Robbins, 2000).

Thus, the observations of the effect of antidepressant medications on executive function appear to largely mimic those seen in studies of psychomotor function. Although TCA drugs appear to have a sedative effect on aspects of executive function, such as information processing, selective attention, and working memory, SSRI medications appear to have a neutral or positive effect on the same measures. The discrepancy in these findings may be attributed to either the increased affinity for serotonin exhibited by SSRIs, or to the nonmonoamine affinities of the TCAs, or perhaps a combination of the effect of both factors.

Memory and learning

Mnemonic function has also been studies in investigations of the association between antidepressant medication and cognitive function. As previously noted in this review, there are various divisions that exist in the human memory system, including a variety of subdivisions within both the short- and long-term stores. Studies of the behavioural impact of AD medication have included measures of both short- and long-term memory, and have extended to include assessment of both semantic and episodic long-term memory.

In his review of the effect of antidepressants on cognition, Amado-boccara suggests that acute administration of TCAs to healthy controls largely appears to have no effect on mnemonic function. This extends to measures of short-term memory, such as the digit span test, and long-term memory, including learning, recognition, and recall of both verbal and visual material. Moreover, in this review a number of SSRI drugs were noted to have no sedative effect on any of the included measures of memory and learning, and none were found to enhance memory function. This pattern of findings was also applicable to the long-term administration of these drugs in normal volunteers (Amado-Boccara et al., 1995).

Although the findings across studies included in the above review were relatively consistent, there is evidence to suggest a potential effect of antidepressants on specific aspects of memory. For example, a study by Harmer and colleagues found that acute administration of citalopram had no effect on the immediate recall of auditory verbal material, but that it induced an enhancement in long-term memory performance in terms of both delayed recall and recognition (Harmer et al., 2002).

In addition, it has also been suggested that the noradrenergic system may play a critical role in the consolidation of emotional memory, namely that blocking the adrenergic system in humans may result in a reduced capacity for the recall of emotionally salient material. However, the findings regarding this hypothesis are not entirely consistent. While an earlier study by O'Carroll found that the administration of an agent which stimulated central noradrenergic activity (i.e. yohimbine) resulted in healthy volunteers recalling more emotional material than participants given an agent that blocked noradrenergic activity (i.e. metoprolol; O'Carroll et al., 1999), a later study found no effect of selective stimulation of the noradrenergic system (i.e. using reboxetine) on long-term memory function (i.e. Papps et al., 2002).

In summary, those studies that have examined the effect of various antidepressant medications on a number of different aspects of cognition seem to imply a relatively consistent profile of cognition associated with different classes of medication. Tricyclic antidepressants reliably impair the performance of normal healthy adults on measures of psychomotor and executive function. This effect has been noted in acute, subacute, and chronic administration of TCAs in normal healthy participants. Selective serotonin reuptake

inhibitors, on the other hand, result in a relative sparing or enhancement of these same functions, again in healthy volunteers, and between acute and different multiple dose administrations. In addition, the administration of either class of medication has not been noted to have any significant or consistent effect on mnemonic function.

A major issue in the majority of studies of the behavioural effect of antidepressants is the fact that most studies employ samples of healthy volunteers. On one hand this does have the advantage of segregating effects on cognition that are due to the medication in question from deficits that are associated with the profile of cognitive dysfunctions associated with MDD. However, it should be noted that there is a possible and likely interaction effect between the symptomatic profile of clinical groups and antidepressant medication. This interaction should be taken into account when estimating the effect of ADs on any measure of cognitive function in the clinically depressed population, based on observations in non-clinical samples.

Although there is a reasonably reliable profile of cognitive function associated with different classes of antidepressant medication, also of interest in the series of investigations that have comprised this study was the potential effect of AD drugs on the neuroimaging data acquired in functional activation studies of major depression. Therefore, the following section of this review will aim to determine the potential effect of antidepressant medications on cerebral metabolism, and their impact on the acquisition of functional neuroimaging data.

1.3.3 Functional neuroimaging studies of cerebral metabolism associated with antidepressant medication

The function of the serotonin extends beyond the regulation of affective behaviour and includes a variety of mechanisms, which extend to a broad range of physiological systems, such as cardiovascular regulation, respiration and thermoregulation, and behavioural processes. Resultantly, the physiological impact of any agent that alters 5-HT function is potentially varied. As already noted, the majority of medications that are currently in use as treatments for major depression do, to some degree, impact upon the level of 5-HT available at receptor sites in the brain. Therefore, of concern in studies of depression is not only the effect that antidepressants may have on the behavioural aspects of the symptom

presentation of depressed individual, but how ADs may impact upon the physiological systems of the patient.

The probability of disruptions in cerebral metabolism resulting from properties of the type of psychotropic medication being taken by patients at the time of testing, rather than being endemic to the experimental group is of particular concern when conducting functional neuroimaging studies, such as fMRI or PET, of clinical populations. Yet, despite this potentially significant confounding factor, there have been relatively few studies of the effect of antidepressants on regional cerebral blood flow. Moreover, the majority of studies have only considered the metabolic effects of medications belonging to the SSRI class of ADs. Nonetheless, consideration of the literature available for different medications within this class should allow for the determination of a model of the potential effect of antidepressant medication on measures of cerebral blood flow.

Fluoxetine

Bonne and colleagues conducted one of the few studies to monitor the effect of chronic administration of AD medication in a sample of normal volunteers. These investigators employed ^{99m}Tc-HMPAO SPECT to determine the blood flow consequences of the consumption of fluoxetine, i.e. 20mg/day for a period of 6 weeks. Using a region of interest approach, the authors aimed to determine whether there were any significant changes in global or regional cerebral blood flow associated with chronic administration of fluoxetine. However, the results of their data analysis revealed no AD associated changes in blood flow, at both global and regional levels of analysis (Bonne et al., 1999). Therefore, they suggested that the changes in CBF seen in previous studies were potentially the result of differences between depressed patients and healthy controls, or between acute and chronic administration of ADs.

A later study by Mayberg also examined the metabolic effects of fluoxetine. However, in this study the authors employed a sample of depressed patients. Mayberg and colleagues were interested in the differential regional metabolic effect of fluoxetine in patients who did and did not respond to AD treatment, i.e. 'responders' and 'nonresponders', respectively. The investigators examined time course changes in brain glucose metabolism in a sample of hospitalised unipolar depressed patients using PET, and noted time specific and response-

specific effects at two different time points, i.e. 1-week and 6-weeks after the commencement of AD medication. It was found that although the pattern of cortical function was similar between responders and nonresponders at 1-week, after 6-weeks there were significant differences between the groups. Responders were characterised by relatively decreased activation in the limbic and striatal regions, and increases in brain stem and dorsal cortical regions (prefrontal and parietal, and anterior and posterior cingulate). Nonresponders, on the other hand, either showed the same pattern of cortical metabolism as they had at 1-week, or failed to show changes in subgenual cingulate or PFC (Mayberg et al., 2000).

Venlafaxine

Two studies by Kalin and colleagues have also examined the profile of regional cerebral metabolism associated with the AD treatment of depressed patients, using venlafaxine (i.e. Kalin et al., 1997; Davidson et al., 2003). Both studies compared the performance of depressed patients to normal controls on a measure of affective processing at baseline, and at a period of two weeks after the commencement of venlafaxine treatment. The second study also examined the relative changes at 8-weeks following the start of medication. Although the patterns of cortical activation were similar between patients and controls at different time points in the first study, in the baseline measurement controls displayed a decreased activation in response to positive stimulus items which was absent in the patients. However, after two weeks of treatment with venlafaxine an area of activation appeared in the right secondary visual cortex of depressed patients in response to positive stimuli (Kalin et al., 1997). Thus, suggesting that the patients' response to treatment was mediated by changes in cortical function, which resulted in the pattern of activation in patients mimicking the activation of controls.

The second investigation by this group also found significant treatment associated changes in cortical activation. The baseline measures from this study revealed a significant difference between patients and controls in the left insular cortex and the anterior cingulate. In both instances the degree of activation in patients was significantly lower than controls. However, after just two weeks of venlafaxine treatment patients a showed relative increase in the insular cortex. Moreover, after eight weeks there was an apparent normalisation in activation in the anterior cingulate (Davidson et al., 2003).

Therefore, both of these studies support the notion of specific alterations in cerebral metabolism as a result of the administration of antidepressant medication. Moreover, in accordance with the Mayberg study, these findings support the notion of an association between these types of changes in regional cerebral blood flow and the likelihood of response to AD treatment.

Sertraline

Metabolic functional neuroimaging has also been employed to examine the association between another SSRI medication, i.e. sertraline, and regional cerebral blood flow. Drevets and colleagues used PET to determine the nature of this relationship in a sample of previously unmedicated MDD patients. Following treatment with sertraline, cortical metabolism significantly decreased in the left amygdala and left subgenual AC of depressed patients. In addition, there was a trend towards a significant difference in post-treatment blood flow in the orbital and posterior cingulate cortices. It was found that these changes were largely limited to those patients who responded to treatment and who remained well at 6-month follow-up. Indeed, the metabolic reduction in the amygdala was significantly correlated with HRSD score (Drevets, Bogers & Raichle, 2002).

Paroxetine

A further study to employ this type of experimental method to examine the association between AD medication and cortical metabolism was a study of the effect of paroxetine on cortical metabolism, conducted by Kennedy and colleagues. In this study, the experimenters assessed the effect of six weeks of paroxetine treatment on frontal and limbic activation in a sample of male depressed patients. Using PET, it was observed that following successful paroxetine therapy patients exhibited increase glucose metabolism in dorsolateral, ventrolateral, and medial aspects of the PFC (i.e. more left, than right, lateralised), the parietal cortex and the dorsal anterior cingulate. Moreover, areas of decreased metabolism were found in both anterior and posterior insular regions (LH), in conjunction with decreases in the right hippocampal and parahippocampal regions (Kennedy et al., 2001). Thus, implying that successful AD treatment was associated with a reversal of the frontal hypofrontality and limbic hyperactivity that are believed to characterise cerebral metabolism in MDD.

In conclusion, the available evidence is indicative of a significant association between consumption of antidepressant medication and both global and regional cerebral blood flow. More specifically, this association appears to be conditional, applying only to those participants with a clinical diagnosis of depression and who also respond to antidepressant treatment. Based on the available evidence, chronic administration of AD drugs appears to have no significant effect on metabolism in normal healthy volunteers. However, given the relative lack of evidence regarding the relationship between blood flow and medication status in healthy adults, it is difficult to draw any definitive conclusions regarding this issue.

Given the rather consistent nature of the evidence supporting the notion that the relative effect of AD medications on cerebral metabolism is an important factor in the nature of the imaging data acquired in studies of MDD, this is an important issue which needs to be taken into account in functional neuroimaging investigations of depressed patients who are not medication naïve.

1.4 Experimental aims and hypotheses

1.4.1 Introduction to experimental aims

There are a number of pertinent points that arise from the consideration of the background literature relevant to the study of cognitive function in major depression. First of all, there is the issue of whether there is a consistent pattern of cognitive impairment associated with major depression, and if so can this pattern be best characterised as a global or specific impairment of cognitive function? Secondly, which factors associated with major depression may be critical factors in the types of cognitive dysfunctions commonly associated with MDD? For example, are cognitive impairments in major depression the manifestation of underlying abnormalities in cortical function? And finally, which factors are of importance in attempting to understand the relationship between major depression, cortical function, and cognitive performance?

The aim of this series of investigations was to attempt to produce experimental evidence that would be useful in answering these questions. In order to achieve this three empirical investigations were conducted. The aims and hypotheses of each of these investigations are outlined in the following sub-sections.

1.4.2 Experiment one: Working memory in depression

Depressed patients may exhibit both qualitative and quantitative changes in how internal and external information is processed, interpreted, and stored (Weingartner et al., 1981). Evidence to support this pattern of dysfunction comes from investigations of a variety of measures of cognitive performance in individuals with a clinical diagnosis of major depression. Deficits have been noted in tasks ranging from elementary processes, such as basic psychomotor function, to the higher cognitive processing required by measures of mnemonic function.

It has previously been suggested that the range of deficits associated with MDD may be the result of abnormalities in executive function in depressed patients, such as would be characterised by a deficit in the central executive component of the human working memory system (Channon et al., 1993). However, there have been relatively few studies of cognition in MDD that have employed specific measures of working memory and the findings relevant to the integrity of WM in depressed individuals are inconsistent, with some

investigations finding little evidence impairment on tests of working memory. Moreover, those studies that have found evidence of a working memory dysfunction associated with the central executive have done so using measures such as the DGB and PASAT, both of which may require the short-term manipulation of information in a manner that is better characterised by models of WM other than the Baddeley and Hitch (1974) model.

In addition, there is also the issue of the considerable variation in the approaches of different studies of the association between MDD and cognitive performance on a number of potentially confounding factors, such as participant age, severity of depression, and diagnostic profile.

Therefore, the aims of the first study were to compare the performance of a clearly defined sample of depressed patients and matched, healthy controls on a measure of working memory that had been shown to accurately assess the manipulation of the central executive component of the working memory system in normal healthy adults, i.e. the n-back task.

The experimental hypotheses in this study were as follows:

1. All participants will experience an increase in difficulty in performance of the n-back task associated with the linear increase in task difficulty; and
2. Depression will be associated with a relative impairment of performance on the n-back task.

1.4.3 Experiment two: Working memory in depression: a functional MRI study

The review of structural neuroimaging studies of major depression revealed evidence of abnormalities in both frontal and striatal regions of cortex associated with MDD. It has been suggested that these structural abnormalities may have a contributory effect to the profile of affective and cognitive symptoms observed in depressed patients.

In addition, functional neuroimaging studies of MDD have implied that the same regions that have been shown to be structurally abnormal are also functionally abnormal in depressed individuals. Moreover, the metabolic dysfunction in specific regions of the

frontal cortex may be critically related to the profile of cognitive dysfunction related to the experience of unipolar depression.

Moreover, there is also considerable overlap in the regions of structural and functional abnormality associated with major depression and those regions that have been noted to mediate working memory function in normal healthy adults, including regions of both dorsal and ventral prefrontal cortex. Thus, supporting the notion of impairment of working memory function in major depression, and allowing for the inference of causal mechanisms in this type of deficit.

Therefore, the aim of the second experiment in this study was to extend the observations of the first study to see if there was a depression associated impairment in the performance of tasks reliant on normal working memory function, and to determine whether any difference in the performance of depressed patients and healthy controls could be attributed to the differences in cortical activation during performance of the n-back task (i.e. as assessed using fMRI).

Based on the observations of previous neuroimaging investigations, the additional experimental hypothesis that was examined in the second experiment was:

3. Relative differences in the performance of depressed patients and healthy controls on the n-back task will be associated with relative differences in the level of cortical activation in those regions putative to normal working memory function.

1.4.4 Experiment three: The effect of escitalopram on working memory in normal healthy adults: A functional MRI study

A main factor of concern in any study of clinical populations is the impact of psychotropic medication upon observed symptomology. Of particular significance in studies of depression is the effect of antidepressant medication on cognition. In the case of unipolar depression, investigations of antidepressant medications on measures of cognitive function have produced mixed results. While some classes of antidepressants, such as the TCAs, appear to have a sedative effect on various aspects of cognition, others types of AD

medication, e.g. SSRIs, seem to produce either no effect or a facilitatory effect on cognitive performance.

However, in functional neuroimaging investigations an additional factor of interest is the effect of any agent consumed by participants on mechanisms that are critical to the acquisition of imaging data, i.e. regional metabolic blood flow. With regards to depressed patients there appears to be a reliable effect of antidepressant medications on cerebral blood flow in treatment responsive patients.

Therefore, it was decided that the consumption of antidepressant medication was an issue that needed to be addressed in the current series of experiments. There were a number of potential ways to deal with this factor that were considered, such as attempting to recruit a control sample of medication-free depressed patients to compare with the original sample of depressed patients who took part in the second experiment. An alternative proposal was the use of follow-up scans for the sample of depressed patients in experiment two during a period of medication-free remission from MDD. However, both of these methodological approaches were rejected due to practical and ethical considerations.

First of all, one of the first courses of action of any physician faced with depressive symptomology in a patient is the prescription of an AD medication. Therefore, the recruitment of individuals who are depressed but not medicated often relies on the use of prospective sampling methods. Although this approach can identify individuals who are significantly depressed there is the potential ethical issue of withholding treatment from individuals who have been identified as being depressed for research purposes. In the case of the second approach, given the small number of participants being scanned in experiment two (i.e. N = 10), the limited timeframe of this project and the likely duration of depression, it was felt that it was unlikely that a reasonable number of previously examined depressed patients would have been in a position to be re-scanned.

Thus, it was felt that the most reasonable approach to this problem was to control for the effects of medication on the cognitive performance of the n-back task and the associated cortical activation in the depressed sample by comparing depressed individuals with a sample of medicated healthy controls on both of these aspects of performance. Although,

the Bonne study was indicative of no effect of chronic administration of AD drugs on cerebral blood flow in normal healthy adults, this represents findings from one investigation only and there is evidence to suggest that there may be an acute dosing response in healthy volunteers. Moreover, there is significant amount of evidence that is suggestive of similarities in the behavioural effects of AD medication in depressed and normal samples (see Amado-Boccara et al., 1995 for a review).

Taking account of these observations, the third, and final, study in this project involved the scanning of normal healthy controls following the subacute administration of an SSRI medication (i.e. escitalopram) and during a medication-free period. As with the previous study, the pattern of cortical activation associated with the performance associated with attempting the n-back task was determined using functional MRI.

Based on previous findings relating to the effect of SSRI medication on cognitive function (i.e. neutral or facilitatory) and cortical activation, the experimental hypotheses that were addressed in experiment three were:

4. Subacute administration of an SSRI medication (i.e. escitalopram) in normal healthy adults will be associated with significant alterations in performance on measures of cognitive function, including working memory.
5. Compared to the medication-free condition, participants in the post-medication condition will experience a relative alteration in the degree of activation in those areas of cortex associated with metabolic changes in treatment responsive depressed patients.

The following chapters outline the methodological approaches used to investigate each of these experimental hypotheses (i.e. Chapter 2, 4, and 6) and the associated outcomes of each study (i.e. Chapters 3, 5, and 7).

Chapter 2: Methodology - Experiment One

2.1 Design

A case control study with a single between subjects factor of participant group (i.e. depressed patients vs. matched, healthy controls) was employed to test the experimental hypotheses (see Chapter 1: pp 89). The within subjects factor was the level of difficulty on the n-back task (i.e. 0-, 1-, 2-, and 3-back). The dependent variable was performance at each level of difficulty of the n-back task. With respect to n-back performance, both mean number of correct responses (i.e. expressed as a percentage of total number of potential responses) and mean reaction time. Both simple group effects and group by task difficulty interactions were of interest.

2.2 Participants

2.2.1 Recruitment

2.2.1.1 Patient recruitment

Ethical approval from the Lothian NHS board, Psychiatry and Psychology Research Ethics Committee, and management approval from the Lothian Primary Care NHS Trust, were obtained for the recruitment of patients of the Royal Edinburgh and associated hospitals to participate in the study. In order to recruit suitable participants a prospective sampling method was employed.

Initially consultants of the Royal Edinburgh Hospital were notified of the study, its aims and proposed method, and the possibility of their patients being approached to participate. They were asked to notify the researchers if they had any objection in principle to the potential participation of their patients in the experiment.

Following the general approval of the consultants ward staff in the general adult mental health wards of the Royal Edinburgh Hospital were contacted regarding the study. An information sheet was given to staff that outlined the details of the investigation and the types of patients that were being sought. This was provided to ward staff along with a copy of the information sheet for patients and contact details for the researchers. The same information was also sent to staff of the outpatient units associated with the hospital.

After the initial contact a number of follow up visits and phone calls were made to ward staff and the day hospitals in order to ascertain whether patients who met the criteria for participation were being treated and whether they would be able to participate in the study.

Potential patients were approached based on the recommendation of a member of staff responsible for their care. Once a suitable patient had been identified a meeting or telephone call with the patient was arranged, in which the nature of the investigation was explained. They were provided with an information sheet with a full outline of the study, and details of individuals who could be contacted regarding the study. Each potential participant was advised to read the information carefully and to discuss participation with those responsible for his or her psychiatric care, as well as friends and family members. After a period of at least 24 hours patients were then re-contacted in order to ascertain whether or not they wished to participate in the study.

2.2.1.2 Control recruitment

Control participants in this study were opportunistically sampled. At the same time as members of ward staff of the Royal Edinburgh hospital were contacted regarding the need for suitable patient participants they were also given an information sheet outlining the need for normal, healthy controls. This form described the need for controls in this type of study, the type of controls that were being sought, and the expectations of those willing to participate in the investigation. The researchers asked staff to recommend any individuals, including themselves, who met the criteria for participation.

Similarly information was circulated in the Division of Psychiatry at the University of Edinburgh regarding the need for healthy controls. Staff and post-graduate students were e-mailed the details of the study and asked to recommend individuals who they felt would be suitable to act as controls.

Through this opportunistic method a number of individuals were identified who met the criteria for inclusion as normal control participants. From those who volunteered a sample was selected of those who it was felt provided the most suitable matches for the depressed individuals who had been recruited to participate. While some of these individuals included staff of the University of Edinburgh, Division of Psychiatry and the Royal Edinburgh

Hospital, it was ensured that none of the control participants were involved in a dependent relationship with either of the investigators. In a similar approach as was adopted with depressed patients interested in participating in the study, potential participants were contacted by the researchers and provided with full details of the project and given the opportunity to ask questions. They were also advised to discuss participation in the study with friends and family, and were re-contacted after a minimum period of 24 hours regarding consent to participate.

2.2.2 Participant details

Participants were twenty individuals with a diagnosis of major depressive disorder and twenty matched normal, healthy controls (see Table 2.1 below). All patients who participated in the project were either in- or out patients (i.e. six and fourteen respectively) of the Royal Edinburgh Hospital, and associated hospitals, within the Lothian Primary Care NHS Trust. These patients were selected on the basis of a diagnosis of major depressive disorder by those responsible for their medical care. In addition, the average length of time since initial diagnosis and length of the current episode was 79.3 and 13.9 months, respectively.

Level of depression at the time of cognitive assessment was determined using the Beck Depression Inventory (BDI) Beck et al., 1961 and the Hamilton Rating Scale for Primary Depressive Illness (HRSD) Hamilton, 1967. It was ensured that depressed patients scored at least 15 on both the BDI and the HRSD, as this was deemed to be indicative of a significant level of depression (see section 2.5: Materials).

Participant Group	*Mean ages (years) (mean(s.d))*	*Mean NART estimated IQ (mean(s.d.))*	*Ratio of Male: Female participants*
Patients	34.65 (8.887)	111.25 (9.233)	4:16
Controls	30.80 (8.889)	117.50 (6.629)	4:16

Table 2.1: Summary of participant demographic details: Experiment One

All participants who participated in this study were required to meet the criteria outlined in Table 2.2. Moreover, control participants were required to have no history of psychiatric illness, although, it should be noted that this information was obtained via self-report and was not corroborated with each individual's own doctor or other individuals.

Inclusion criteria: All participants	*Inclusion criteria: Patients only*
Aged 18 – 50 years old. No history of serious physical health problems, including diabetes, liver disease, heart attack, and stroke. No history of head injury No history of alcohol or drug misuse Not colour blind Not pregnant	No history of psychotic symptoms No medication change in the 7 days preceding participation No electroconvulsive therapy in the 6 months preceding participation

Table 2.2: Criteria for inclusion - Experiment One

Within the depressed sample eighteen patients were taking anti-depressant medication at the time of testing (see Table 2.3). Of the two patients who were not currently taking medication for their illness, one patient had been medication free for two weeks and the other for three months. Furthermore, five participants were also taking additional medication at the time of participation. The combinations of medication being consumed by patients not only included anti-depressant but also other classes of psychotropic medication (see Table 2.4).

2.2.3 Excluded/Withdrawn participants

An additional eleven patients were recruited for the study but failed to either commence or complete testing. Four of these depressed patients were withdrawn from the study due to failure to meet our minimum BDI and HRSD requirements. In the remaining sample of six, one patient was recruited but discharged from the hospital prior to testing phase, and did not respond to numerous attempts to contact her. In addition, three patients experienced a catastrophic reaction during testing, and were unwilling to rearrange alternative testing sessions. The final patient in this sub-group was omitted from the study due to a change in diagnosis after recruitment but prior to testing.

Furthermore, one patient and one control participant completed testing but it was later observed that there had been an error in the data acquisition for the n-back task for both of these subjects. We were unable to rearrange testing sessions for these two participants, and thus their other data was excluded from the final analyses.

It should also be noted that an additional male participant was recruited in the pilot stages of the study. However, the patient's age exceeded our upper limit (i.e. he was 59 years old) and although the patient did complete all testing sessions, his data has not been included in any of the analyses.

Name of Medication	*Number of participants*
Clomipramine	2
Fluoxetine	1
Imipramine	2
Mianserin	1
Mirtazapine	2
Paroxetine	2
Reboxetine	1
Trazodone	1*
Venlafaxine	7

Table 2.3: Details of anti-depressant medications being consumed by depressed patients at the time of participation - Experiment One
(* This participant was also taking venlafaxine)

Anti-depressant medication	*Additional medications (medication (classification))*
Clomipramine	Thioridazine (neuroleptic), Zoplicone (hypnotic)
Mianserin	Amisulpride (neuroleptic), Lamotrigrine (anticonvulsant)
Mirtazapine	Procycladine (anti-Parkinsonian)
Paroxetine	Temazepam (benzodiazepine)
Venlafaxine	Medazepam (benzodiazepine)
Venlafaxine, Trazodone	Diazepam (benzodiazepine)

Table 2.4: Combinations of medication being consumed by those patients who were prescribed more than one medication at the time of participation - Experiment One

2.3 Materials (see Appendix 2)

2.3.1 Pre-test materials

Participant information sheet

As noted above, prior to participation all participants were provided with a copy of an information sheet for participants (see Appendix 2). Participants were given the information sheet a minimum of 24 hours prior to participation, and were advised to consult with friends, family, and (in the case of patients) those responsible for their medical care before deciding whether or not to participate in the study. Individuals were also advised that they were at liberty to discuss any questions or queries that they had with either of the investigators.

Consent form

Participants were asked to sign a consent form prior to participation, which outlined the conditions of testing. In addition, it was verbally reiterated to all participants that participation in the study was on an entirely voluntary basis, and was completely independent of current or future treatment as a patient of Lothian Primary Care NHS Trust. Participants were also advised that agreement to participate did not imply commitment to complete testing, and that they were free to withdraw at any stage during the study, without giving a reason. For all participants there was a copy of the signed consent form for the participant and one for the investigators. Patients were asked to sign an additional copy of the consent form, which was later appended to their medical records.

Once informed consent had been obtained participants were asked to complete the following pre-test measures, which had been compiled in order to determine the suitability of a particular candidate for participation.

Medical questionnaire

Initially individuals were asked to complete a medical questionnaire. Two copies of this questionnaire were prepared, i.e. one for patients and one for controls. Each version of the questionnaire posed questions relating to each of the relevant inclusion criteria for patients and controls, e.g. 'Have you ever had a head injury?' Participants were also asked to impart any additional information that may have excluded them from participation in either this or future phases of the project, e.g. whether or not they were colour blind, or whether or not they were currently pregnant.

Patient information sheet

For all patients who participated in the study a member of staff involved in their medical care was asked to complete a 'Patient Information Sheet' (see Appendix 2). Information obtained in this form was used to support patient statements with regards to details which may possibly have excluded them from participation in the study, e.g. a history or drug or alcohol abuse. For some patients this information was determined from medical notes provided by staff members.

2.3.2 Affective indices

Participants were required to complete a number of affective assessments prior to testing. All participants completed the Beck Depression Inventory Beck et al., 1961, the Stress Arousal Checklist Mackay et al., 1978, and the Alderley Park State Anxiety Questionnaire Walker, 1990. In addition, patients were also retied on the Hamilton Rating Scale for primary depressive illness Hamilton, 1967.

Beck Depression Inventory (BDI; Beck et al., 1961)

A full description of the BDI and the appropriate procedure can be found in Beck et al., (1961). Briefly, the BDI consists of 21 items that deal with various aspects of depressive symptomology, e.g. mood, sense of failure, sleep disturbance etc. Participants are asked to indicate which of 4 statements allocated to each item most accurately describes their emotional state at the time of testing and over the preceding 7 days. The statements associated with each item are allocated a score from 0 – 3. Each statement is scored in such a way that the higher scores are indicative of greater severity of the symptom in question. For example:

Item 1: Mood
1. I do not feel sad (0)
2. I feel sad (1)
3. I am sad all the time and I can't snap out of it (2)
4. I am so sad or unhappy that I can't stand it (3)

The statements for each item can be read aloud to participants, with participants then asked to indicate to the experimenter which item they feel is the most accurate description of their mood. Alternatively, the assessment can be self-administered. The latter approach was employed in this particular investigation. However, a researcher was available during completion of this task in the event that participants experienced difficulty in understanding the statements or were unsure of how to respond.

Individuals were advised as to how to complete the assessment by the investigator, i.e. to read through each of the items, and to select (by circling the relevant statement number) the statements in each item that they felt best describes how they were feeling 'today' and have

been feeling for the previous 7 days. Participants were also advised that if they felt unable to decide between two statements for a particular item then they should circle both statements.

In accordance with the instructions for rating the BDI, participants are allocated a score based on the sum of the statement scores for all of the items. In those instances where a participant selects two statements for the same item the statement with the greater allocated score is selected for inclusion in the overall rating. The following interpretation guidelines were used in this study:

Score range	*Indication*
0 – 9	Normal range
10 – 15	Minimal depression
16 – 19	Mild – moderate depression
20 – 29	Moderate – severe depression
30 – 63	Severe depression

Table 2.5: Interpretation guidelines for the BDI. Adapted from Beck (1987). (From the Beck Depression Inventory)

Based on the above guidelines, a BDI score of less than 9 was deemed appropriate for control participants. Whereas, a score of greater than 15 was determined to be the minimum accepted score for patients.

Hamilton Rating Scale for primary depressive illness (HRSD; Hamilton, 1967)

A full description of the HRSD and its administration can be seen in Hamilton (1967). The HRSD consists of 21 open ended questions, again relating to various aspects of depressive symptomatology. Either a trained clinician or researcher carries out the assessment. For each question there is a guide to the types of response that may be given, and how each category of response should be scored. For example:

Item 1: Depressed Mood
Researcher prompts: What's your mood been like this week?
Have you been down or depressed?
Sad? Hopeless?
In the last week, how often have you felt (OWN EQUIVALENT)?
Every day?
Have you been crying at all?
How long have you been feeling this way?

Score:

0 – absent
1 – indicated only on questioning
2 – spontaneously reported verbally
3 – communicated non-verbally, i.e. racial expression, posture voice, tendency to weep
4 – VIRTUALLY always: this is spontaneous verbal and non-verbal communication

The absence of a particular symptom is always rated as 0 and the maximum score for each item can vary from 2 – 4. As with the BDI, the overall rating for the HRSD is calculated by summing the score allocated for each of the items.

It has been noted (i.e. Frank et al, 1991) that a score of ≤ 7 on the HRSD should be deemed as asymptomatic, whereas a score ≥ 15 is indicative of an individual being symptomatic for major depressive illness.

Stress Arousal Checklist (SAC; Mackay et al., 1978)

The SAC is used as a measure of state stress (see Mackay et al., 1978; Cox & Mackay, 1985). The checklist is underpinned by a two-dimensional model of mood (i.e. Cox & Mackay, 1985). The first dimension relates to feelings of unpleasantness/pleasantness or hedonic tone (i.e. stress) and the second to wakefulness/drowsiness or vigour (i.e. arousal).

Respondents are presented with a list of 30 different mood adjectives (e.g. 'tense', 'relaxed' etc). Fifteen of these adjectives are 'positive' and fifteen are 'negative'. Furthermore, each adjective is accompanied by four different response choices, i.e. ++, +, ?, and -. Twelve of the items relate to the arousal dimension of the model, with the remaining 18 items relating to the stress dimension. Participants are asked to rate whether or not the adjective describes how they are currently feeling, by circling the appropriate response, i.e. definitely → ++, more or less → +, not sure/can't decide → ?, definitely not → -.

The recommended scoring of the checklist is to allocate a score of 1 for each ++ or + response, and a score of 0 for ? or – responses for negative adjectives. Positive adjectives, on the other hand, are allocated a score of 1 for a ? or – response, otherwise a score of 0 is allocated. Thus resulting in a range of scores on the stress scale of 0 – 18, and a range of 0 – 12 on the arousal scale.

Alderley Park State Anxiety Questionnaire (APSAQ; Walker, 1990)

This particular questionnaire is administered in order to estimate state anxiety. Participants are asked to respond to 12 items relating to state anxiety. There are 5 'positive' and 7 'negative' statements (e.g. 'I feel I can cope' and 'I am worried', respectively). Participants are asked to indicate the extent to which each of the statements corresponds to how they are currently feeling, i.e. 'not at all', 'slightly', 'moderately',' considerably', or 'extremely'. Thus the potential score range for each item is 0 – 5. For each type of statement (i.e. positive or negative) the following scores are allocated for each category of response:

Statement Type	*Response*				
	Not at all	Slightly	Moderately	Considerably	Extremely
Positive	5	4	3	2	1
Negative	1	2	3	4	5

Table 2.6: Response ratings for positive and negative items on the APSAQ

Therefore, the maximum potential score on the APSAQ is 60, with a high score being indicative of a high level of state anxiety.

2.3.3 Cognitive assessments

National adult reading test (NART; Nelson & Willison, 1991)

The NART was used employed in order to estimate the WAIS-R (Wechsler, 1981) full scale IQ of control participants and the premorbid IQ of the depressed patients). Full details of the procedure for the NART, normative data, and WAIS and WAIS-R IQ estimations can be found in the NART test manual (i.e. Nelson & Willison, 1991) .

The NART is composed of 50 'irregular' English words, i.e. words that do not conform to typical or common rules of grapheme-phoneme representation and pronunciation, e.g. naïve. In order to complete the task participants are simply asked to read aloud the list of words to the experimenter, and are allocated a score equal to the total number of errors that they make. The predicted equivalent full scale, verbal, or performance IQ can then be estimated based on the number of errors committed by the participant – e.g. 20 errors → estimated WAIS-R full scale IQ = 106.

Test of Everyday Attention (TEA; Robertson et al., 1994)

The TEA is a test battery designed to assess performance of everyday tasks reliant on normal attention function, e.g. searching a map for certain symbols. Each of the subtests of the TEA has been designed to assess a specific type of attention, i.e. the map search task is designed to assess selective attention. It is assumed that in normal, healthy adults accurate performance of each of the subtests is reliant on frontal lobe function.

In order to allow for re-testing of participants on each of TEA tests, there are three versions of the test battery available, i.e. versions A, B, and C. Each of these versions of the TEA consists of 8 separate subtests, two of which were employed in the current study. The two subtests used in this investigation were the 'Elevator Counting with Distraction' and 'Visual Elevator' tasks.

- Elevator counting with distraction (ECD)

In this particular test of attention participants are asked to imagine that they are to count the number of floors that an elevator ascends by counting the number of low tones that they hear in a series of mixed tones, i.e. both high and low. Therefore, in order to perform the task accurately the participant needs to ignore the high tones in each series. This task has been designed to assess auditory selective attention and is understood to load on a factor auditory-verbal working memory.

- Visual elevator (VE)

As with the ECD task, the VE assessment of attention function is essentially a counting task. Participants are presented with a series of pictures (i.e. ten). Each picture in the series consists of a number of pictures of a pair of elevator doors, interspersed with both 'up' and 'down' arrows. Participants are asked to determine which floor the elevator will stop at by counting the number of pictures of doors. They are asked to start by counting 'up', starting at the first floor. However, each time they encounter an up or down arrow they need to determine whether to continue or reverse the direction of the lift. Thus, the VE subtest has been designed to assess attentional switching and hence cognitive flexibility. In addition, it has also been shown that the number of correct items on the VE task loads on the same attentional switching factor as the number of categories in the WCST (Robertson et al., 1994).

Performance on the VE is defined by both the number of correct items, and the average reaction time per attentional switch for correct items.

For each of these subtests participants are allocated a score based on the number of items that they respond correctly two (i.e. maximum possible score = 10, in both cases). The raw scores for participants are then adjusted to allow for the age of the participant. This is achieved by allocating the participant a 'scaled score', which is based on their raw score and their age group (these scaled scores are available in the test manual). For example, a 25-year-old participant obtaining a raw score of 6 on the ECD would be given a scaled score of 7, etc.

In addition to a score for accuracy, in the VE task participants are also allocated a score based on the average time taken per attentional switch for each correct item (i.e. in seconds). This raw timing score is also converted to a scaled score based on the participant's age group, e.g. a 45-year-old participant averaging 4.4 seconds/switch would be allocated a scaled score of 8.

Both the VE and ECD subtests of the TEA have been shown to have reasonable test/re-test reliability. Using a one-week test-retest approach, with both normal controls and stroke patients, the following correlation coefficients were obtained:

Subtest	*Pearson Correlations*		
	Normal Controls (N = 118): Version A with B	Normal Controls (N = 39): Version B with C	Stroke patients (N = 74): Version A with B
Elevator counting with distraction	0.71	0.68	0.83
Visual elevator – raw accuracy score	0.71	0.76	0.90
Visual elevator – timing score	0.79	0.70	Not calculated

Table 2.7: Pearson correlation coefficient data for participants tested on either version A then version B of the TEA, or version B then version C, in a one week test-retest approach (adapted from TEA Test Manual; Robertson et al., 1994).

The n-back task

- Paradigm design in imaging studies

Given that this study was conducted as a pilot to the main functional imaging experiment it was essential that the working memory paradigm employed was suitable for use in both neuropsychological and neuroimaging studies. There are a number of potential approaches to paradigm design that can be utilised in functional imaging studies, including subtractive, factorial, conjunction and parametric designs (see Figure 2.1). Therefore, it was important to ascertain which type of experimental design would result in a paradigm that was not only suitable for this initial study but would give us the best chance of obtaining meaningful data in latter investigations.

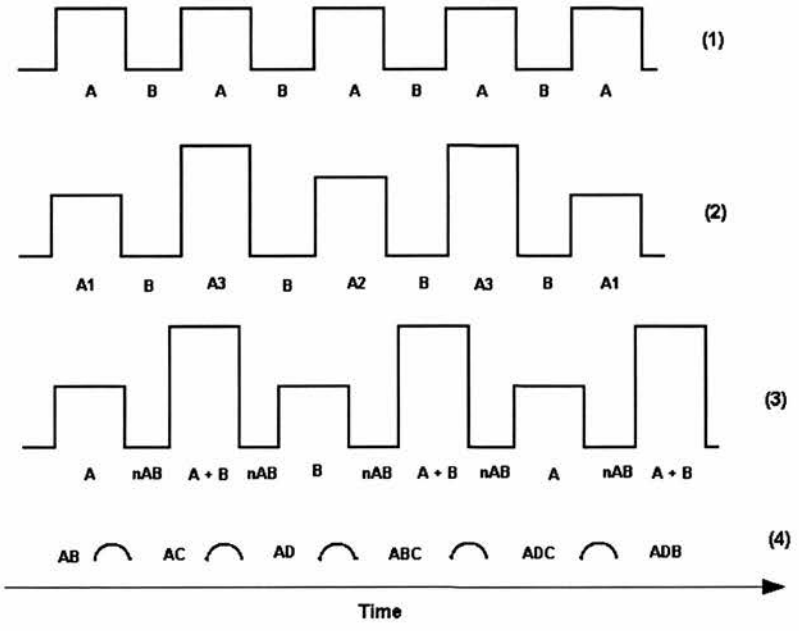

Figure 2.1: Illustration of the various approaches to paradigm design in functional imaging studies: (1) Subtraction, (2) Parametric, (3) Factorial, (4) Conjunction. In all images process 'A' is the process of interest.

The prototypical design employed in functional imaging studies is the 'subtraction' paradigm. In this approach the first step is to design two cognitive tasks (e.g. tasks A and B) that are identical apart from the fact that one contains the cognitive process of interest. The cortical activation associated with this process is then determined through examination of the differences in the activation associated with performance of the two tasks, i.e. the

assumption being that any significant changes observed in the task containing the process of interest but not in the 'control' task are those associated specifically with this process.

While subtraction provides a relatively simple approach to the issues of paradigm design there are potential flaws with adopting this approach. The most commonly cited issue in the problem of 'pure insertion', i.e. there is an assumption that addition of the process of interest does not impact upon the nature of the activation seen during performance of the experimental task. However, it is entirely likely that in the experimental task this change may bring about more fundamental changes in the other cognitive processes required to complete the task, and it may indeed be these alternative changes that are the cause of the differences in activation seen between the two different tasks.

An alternative approach to subtraction is 'parametric' paradigm design. In parametric paradigms, rather than comparing the absolute differences between two tasks, a single task is designed which has an initial baseline level followed by additional task levels of increased difficulty (e.g. A1< A2 < A3) – i.e. there is variation around a single parameter in the task. Given that the processes involved in each level of the task are essentially the same the issue of insertion is removed.

'Factorial' paradigms, on the other hand, examine the interaction between two different cognitive processes of interest (e.g. process A and process B). In such designs tasks are designed which involve either process A or process B or both processes. The paradigm is constructed in such a way that participants undertake one of these possible task conditions interspersed with a condition that involves neither process of interest (i.e. nAB). One of the main advantages of this approach is that it allows investigators to examine the possibility of interaction between different cognitive processes (e.g. where A – nAB <> (A + B) – B).

The final approach to paradigm design is the 'conjunction' approach. This strategy may be employed in those instances where investigators are not interested in the possibility of interaction between distinct cognitive processes. Essentially conjunction paradigms involve a series of categorical subtraction experiments, where each experiment is aimed at isolating the same process (e.g. process A). However, unlike regular subtraction paradigms the

experimental and control conditions do not only differ in the process of interest but in several other processes as well.

While both conjunction and factorial designs reduce the likelihood of the problems associated with subtraction they do not completely eliminate the chance. Parametric paradigms, on the other hand, apparently appear to overcome this issue completely. Therefore, given that we were concerned with only one cognitive process (i.e. central executive function) it was decided that the most suitable type of paradigm to employ in this series of experiments would be a parametric one.

- Design of the n-back task (details of the background of the n-back task can be viewed in Chapter 1: section 1.2)

The n-back paradigm was chosen as a measure of working memory function in this series of studies for a number of reasons. A primary reason for this choice of paradigm was its previously demonstrated reliability, i.e. both behavioural and functional, in assessing working memory ability in normal healthy volunteers. Moreover, the parametric nature of the n-back task was deemed to be appropriate for enabling the more sensitive examination of working memory function in MDD patients, i.e. by manipulating the level of cognitive load it should be possible to determine not only if depression is associated with a dysfunction of WM but to extent of this deficit. Finally, the fact that the n-back paradigm can be easily manipulated, based on the demand characteristics of the study, but still retain the factors that contribute to its reliability, also made it a suitable paradigm for the measure of working memory function in this project.

As we were dealing with a population who were potentially significantly cognitively impaired at the time of testing, it was felt that a delayed match-to-sample task variation might prove too taxing for the patient sample. Therefore, a variation of the n-back task was developed which is reliant on immediate recall ability for a single stimulus item only.

In our version of the n-back task participants were presented with a series of pictures, each consisting of four numbered boxes with a coloured dot in one of the boxes (see Figure 2.1). Participants were then asked to either press the button corresponding to the current position of the dot (i.e. Shadow/0-back), or to press the button corresponding to where the dot was in

(A) the previous picture (i.e. 1-back), or (B) two pictures previously (i.e. 2-back), or (C) three pictures previously (i.e. 3-back). In accordance with normal parametric paradigm design, it was presumed that the shadow task, while relying on the same perceptive and motor functions as the other levels of the task, did not have the same reliance on normal working memory function. It was assumed that by increasing the number of intervening items between presentation and recall we would increase the memory load on the central executive, thereby increasing task difficulty in a parametric fashion.

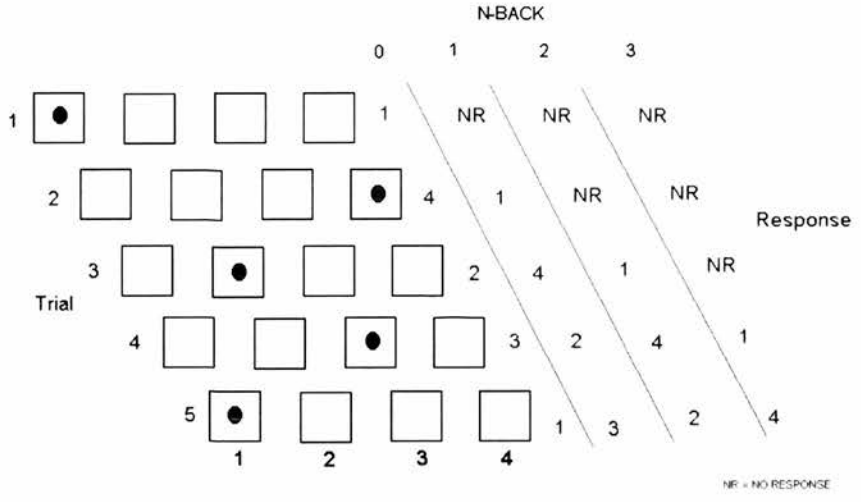

Figure 2.2: Illustration of the levels of n-back employed in the current series of experiments

The task was developed using E-prime (Beta 4) software (Psychology Software Tools Inc., Pittsburgh, PA), and was presented on a workstation running Windows 98 operating system.

2.4 Procedure

All participants were tested on an individual basis. Although the majority of participants were tested at the Division of Psychiatry, a number of the patient sample were tested in a quiet room in a ward at the Royal Edinburgh Hospital, as a result of their conditions of stay at the hospital.

In order to protect participant anonymity prior to testing each participant was allocated a participation code, which was largely based on his or her experimental group. All paper and electronic data for each participant was recorded using this code. Furthermore, any

electronic data containing personal details of participants was password protected. Consequently, the data was stored and analysed in such a way as to make it impossible for other individuals to identify the contribution of specific individuals to the data profile of their experimental group.

Participants were first of all required to complete each of the relevant pre-test measures (see above). Based on these assessments participant suitability was judged. Participants meeting each of the inclusion criteria then proceeded to complete each of the affective and cognitive assessments outlined above.

2.4.1 Affective assessments

The first assessment that all participants undertook was the BDI, which, as previously noted, was self-administered. Participants were advised to read each set of statements carefully, and to circle which of the four statements presented most accurately described how they were 'currently' feeling (i.e. at the time of testing) and had been feeling for the preceding 7 days. Although each participant was advised to select only one statement in each item, if participants enquired what they should do if they felt that they could not decide between two statements they were advised to circle both items.

As noted above, participant's scores were based on the sum of the statement numbers that they selected for each of the 21 items. Where participants had selected two statements, the higher value statement was included in this calculation. Any control participant scoring > 7, and any patient scoring < 15 on the BDI were then excluded from the study.

Following completion of the BDI, participants were then asked to complete the SAC. They were advised that they should circle the response for each adjective that was the most accurate description of how they were feeling 'now', i.e. at the time of testing. They were also advised to try and complete the assessment as accurately as possible, and to try and go with their first response to each adjective. Participant scores for each of the two scales, i.e. stress and arousal, were then calculated as outlined above.

The next assessment that participants completed was the APSAQ. As with the BDI and the SAC this questionnaire was self-administered. In accordance with the normal procedure for

the APSAQ, participants were asked to indicate, by ticking the relevant response box, how they were 'currently' feeling. Participant scores were then calculated as outlined above.

After completion of the other three affective indices, the HRSD was then administered to patients by either a trained clinician or researcher. Each patient was informed that the assessment took the form of structured interview, and that the interviewer would be asking him or her questions relating to various aspects of their depressive illness. Patients were advised to answer the questions based on how they were feeling at the time of testing and had been feeling for the preceding week. Again, they were advised to answer all questions as accurately as possible. Following completion of the HRSD, patient scores were calculated for both 17 and 21 items.

2.4.2 Cognitive assessments

Test of everyday attention

First of all participants undertook the ECD subtest of the TEA (i.e. version A). The auditory tones for each stimulus set were presented using the standard tape cassette (provided by Thames Valley Test Company). Participants were instructed to listen carefully to each set of tones and to count the number of low tones that they heard in each set while ignoring the high tones.

In order to ensure that the nature of the task was entirely explicit participants were given the opportunity to practice the task using two example stimuli sets. The first of these was counted aloud with the researcher. Once it was ensured that the individual in question properly understood the nature of the task participants then attempted the second practice item on their own. Each individual was given the opportunity to repeat each of these practice items until both the participant and the researcher were confident that the experimental trials should begin. There were ten experimental trials, and each participant was allocated an ECD score based on the number of correct responses.

Following completion of the ECD, participants also attempted the VE task (i.e. version A). The nature of the task was explained to the participant, i.e. that they were required to determine the destination floor of the elevator, by counting the number of floors that the elevator either ascended or descended. Participants were then shown two examples of the

test stimuli (see test manual for details). The experimenter ran through the first example with the participant until it was apparent that the participant fully understood the nature of the task. The participant was then given the opportunity to attempt the second practice item by him/herself. As with the ECD task, participants were free to practice both of the example items until they felt comfortable starting the experimental trials.

Participants were advised to attempt all ten of the experimental trials, and that they should begin each new trial only when they felt ready. They were also informed that the task would be timed and that they should complete each experimental trial in as quickly as possible.

Each participant was allocated a score based on the total number of correct trials and a score for the average time taken to make each attentional shift for the number of correct items. The latter score was calculated by summing the total time taken for all correct items and dividing it by the sum of the number of switches for those same items. Once the raw scores for both TEA subtests had been obtained for each participant the relevant scaled score was also noted and both scores were recorded.

The n-back task

Participants were given a verbal description of the n-back task prior to commencing the experimental task. The n-back program was then started and participants viewed a number of instruction screens that outlined the nature of the task in greater detail. Moreover, the instruction screens included visual illustrations of each of the levels of task difficulty, i.e. Shadow/0-back, 1-back, 2-back, and 3-back. Each individual was then given the opportunity to practice each of the different task levels. These practice trials consisted of a single block each of 1-, 2-, and 3-back trials with a block of the shadow task between each subsequent level of the task.

Following the practice phase, and once it was ensured that the competently understood the task, participants began the experimental trials. Individuals were required to perform a total of ten blocks each of 1-, 2-, and 3-back conditions, with each n-back block being separated by a block of shadow/0-back. These experimental blocks were presented in the following order:

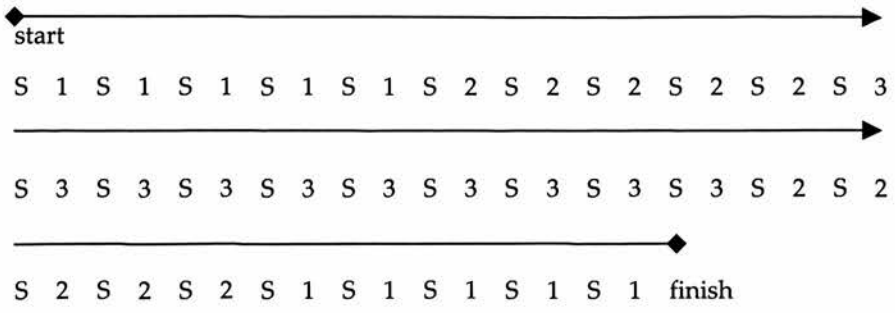

Figure 2.3: Running order for n-back blocks in the n-back task, i.e. S = shadow, 1 = 1-back, 2 = 2-back, 3 = 3-back

Each experimental block consisted of 10 stimulus items, which were each displayed for 3 seconds (i.e. inter-stimulus interval (ISI) = 3 sec.). Therefore, the duration of each n-back block was equal to 30 seconds. Consequently, the ideal running time for the completion of the entire task was just over 30 minutes. However, each of the n-back blocks was preceded by a prompt screen, which informed participants which version of the task they were to perform, e.g. "ONE – BACK", and in order to begin each of the experimental blocks (i.e. to move past the prompt screen) the participant was required to press the space bar. Therefore, if a participant felt the need to take a short rest between trials then they had this option. In fact, prior to testing participants were advised that if they felt the need for a rest between each of the blocks they should feel free to do so. It was felt that this might aid performance of the entire task for patients given that they may have had an exaggerated difficulty in maintaining concentration for such extended periods of time. As a result, the actual time taken for each participant to complete the n-back task varied between subjects. Nonetheless, it should be noted that in most instances participants chose not to dwell on the prompt screens for any extended period of time.

2.4.3 Data Analysis

All of the data obtained in this study were analysed using SPSS for Windows (Release 11; SPSS Inc.). A number of individual analyses were carried out, which will be fully outlined in the following results section (i.e. Chapter 3). However, the two main analyses were two 2 x 4 mixed ANOVAs, which considered the effect of experimental group (i.e. patient or control) and level of task difficulty (i.e. 0-, 1-, 2-, or 3-back) on performance on the n-back task, both in terms of accuracy (i.e. percentage of correct responses) and reaction time.

Chapter 3: Results - Experiment One

3.1 Affective Assessments

	Patients		*Controls*		*Mean Difference*
	Mean (s.d.)	Min-Max	Mean (s.d.)	Min-Max	
HRSD	23.90 (5.79)	11-34	N/A	N/A	N/A
BDI	33.25 (11.38)	15-51	2.15 (2.11)	0-8	31.10
SAC – Stress	12.85 (5.89)	0-18	3.50 (4.26)	0-13	9.35
SAC – Arousal	9.15 (3.48)	1-12	3.70 (2.72)	0-7	5.45
APSAQ	38.00 (9.81)	20-53	19.10 (3.19)	13-25	18.90

Table 3.1: Mean scores on each of the affective assessments: 20 patients vs. 20 controls (Experiment one).

Independent samples t-tests revealed a significant difference in the scores of patients and controls for the BDI (i.e. $t_{(20.305)} = 12.02$, $p < 0.001$), for both the stress and arousal dimensions of the SAC (i.e. $t_{(38)} = 5.75$ and $t_{(38)} = 5.52$, $p < 0.001$, respectively), and for the APSAQ (i.e. $t_{(22.984)} = 8.19$, $p < 0.001$), with patients scoring significantly higher than controls on all of these measures.

However, the distribution of scores, using Shapiro-Wilks (S-W) tests of normality, for each of the affective measures deviated significantly from a normal distribution (i.e. S-W $_{(40)} = 0.85$, S-W $_{(40)} = 0.85$, S-W $_{(40)} = 0.91$, & S-W $_{(40)} = 0.89$, $p < 0.001$ for BDI, SAC-stress, SAC-arousal, and APSAQ, respectively). Therefore, in order to assess the reliability of the t-test results, each of these measures were also subjected to non-parametric analysis, i.e. Mann-Whitney U-test.

The Mann-Whitney U-test also revealed a significant effect of participant group on each of the affective measures, i.e. BDI $U = 0.00$, $p < 0.001$, SAC-stress $U = 46.50$, $p < 0.001$, SAC-arousal $U = 50.00$, $p < 0.001$, and APSAQ $U = 10.50$, $p < 0.001$.

Therefore, we can conclude that patients did not only exhibit higher levels of depressive symptoms, as indicated by the significant difference in the BDI scores between participant groups, but they were also experienced higher levels of state stress, arousal and anxiety at the time of testing.

3.2 Test of Everyday Attention

3.2.1 Elevator counting with distraction

Analysis of performance on the elevator counting with distraction subtest of the TEA, i.e. independent samples t-test, revealed a significant difference between patients and controls in mean number of correct items. This difference in performance between groups was apparent in both the raw data and the scaled scores (i.e. $t_{(31.08)} = 2.57$, $p = 0.015$ and $t_{(38)} = 2.32$, $p = 0.026$, respectively).

3.2.2 Visual Elevator

3.2.2.1 Accuracy

As with the elevator counting with distraction task, there was a significant difference between the experimental groups in mean accuracy (i.e. number of correct items) on the visual elevator task. Again, a significant difference was evident both in the raw data and in the scaled scores for each group (i.e. $t_{(25.03)} = 3.07$, $p = 0.005$ and $t_{(38)} = 2.76$, $p = 0.009$).

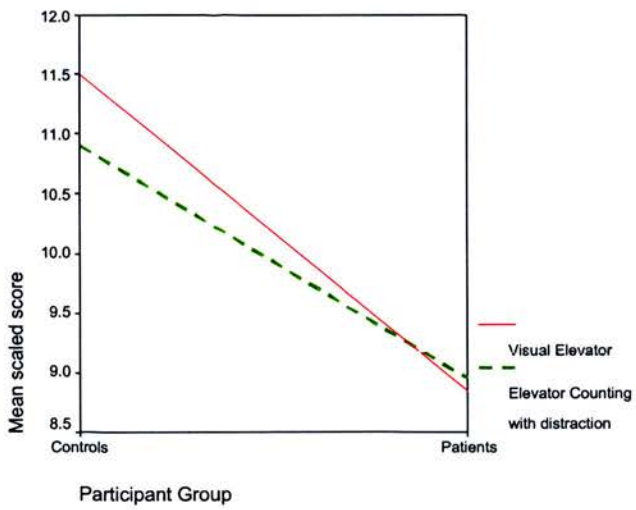

Figure 3.1: Average number of correct items (scaled) on each of the TEA subtests – Experiment 1 (20 controls vs. 20 patients)

3.2.2.2 Timing

In addition to the significant differences between patients and controls in the number of correct items in each of the TEA subtests, the analysis further revealed a significant difference between groups in mean reaction time (i.e. time per attentional switch for correct items) on the visual elevator task. As with the other TEA measures, this significant

difference was noted in both the mean of the raw reaction time scores and the scaled scores (i.e. $t_{(22.21)} = -4.92$, $p < 0.001$ and $t_{(38)} = 5.44$, $p < 0.001$).

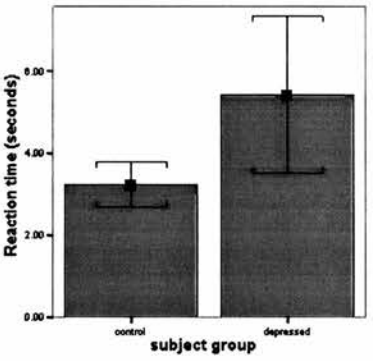

Figure 3.2: Mean reaction time (seconds) per attentional switch on the visual elevator task - Experimen One (20 patients vs. 20 controls)

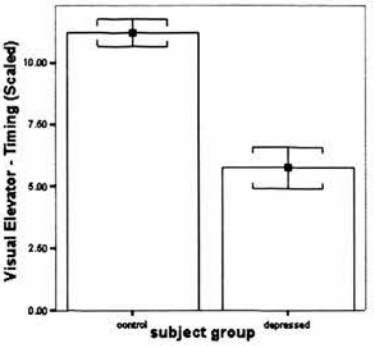

Figure 3.3: Mean scaled score on the visual elevator task - Experiment One (20 patients vs. 20 controls)

However, while the scaled scores for the timing scores on the visual elevator task were normally distributed (i.e. S-W $_{(40)} = 0.98$, $p = 0.557$), it was noted that for accuracy on both the elevator counting with distraction and the visual elevator tasks the distribution of scaled scores deviated significantly from a normal distribution (i.e. S-W $_{(40)} = 0.92$, $p = 0.007$ and S-W $_{(40)} = 0.90$, $p = 0.002$). Therefore, in order to determine the reliability of the findings outlined above, the accuracy data (i.e. scaled) from each of these was analysed using a suitable non-parametric test, i.e. Mann-Whitney U-test.

These analyses also revealed a significant difference between patients and controls with regards to the number of correct items on both the elevator counting with distraction (i.e. $U = 126.00$, $p = 0.46$) and visual elevator (i.e. $U = 112.50$, $p = 0.017$) tasks.

It can, therefore, be concluded that patients performed significantly worse than controls on both the elevator counting with distraction and visual elevator tasks, i.e. in both tasks the mean number of correct items was significantly lower for patients than controls.

Furthermore, patients were also significantly slower than controls to perform correct items in the visual elevator task. This was evident in both the mean time per attentional switch in this task and the scaled scores for each group.

These observations are indicative of impaired selective attention and cognitive flexibility in individuals with major depression. Furthermore, they support the notion of a dysfunction of auditory verbal working memory and psychomotor slowing in the patient group.

3.3 n-back task

As previously noted, the effects of interest in terms of performance of the n-back task were the main effect of participant group (i.e. patients vs. controls) and level of task difficulty (i.e. 0-, 1-, 2-, and 3-back). In order to assess the effect of each of these factors two 2 x 4 mixed ANOVA's were conducted, i.e. one analysis concerned with accuracy (i.e. percentage correct) and one concerned with reaction time (ms) on the n-back task.

3.3.1 Accuracy

As a result of the order of presentation of stimulus items, participants responded to a greater number of 0-back trials than any other n-back level. Therefore, rather than comparing participants raw scores, scores at each level of n-back were converted to percentage scores. The percentage correct for each participant and each level of n-back was then used for the data analysis.

Analysis of the percentage correct at each level of n-back revealed a significant main effect of level of n-back (i.e. $F_{(1.71, 65.13)} = 41.68$, $p < 0.001$) and a significant main effect of participant group (i.e. $F_{(1,38)} = 5.93$, $p = 0.02$). However, there was no significant interaction between these two factors (i.e. $F_{(1.71, 65.13)} = 1.96$, $p = 0.156$).

Post-hoc paired sample t-tests were conducted to determine between which levels of n-back there were significant differences in performance (i.e. percentage correct) across the participant groups. After Bonferroni correction for multiple comparisons (i.e. revised critical value of $p = 0.0167$) it was determined that there was a significant difference between performance at 0- and 1-back (i.e. $t_{(39)} = 2.25$, $p = 0.015$), 1- and 2-back (i.e. $t_{(39)} = 8.08$, $p < 0.001$), and between 2- and 3-back (i.e. $t_{(39)} = 4.15$, $p < 0.001$).

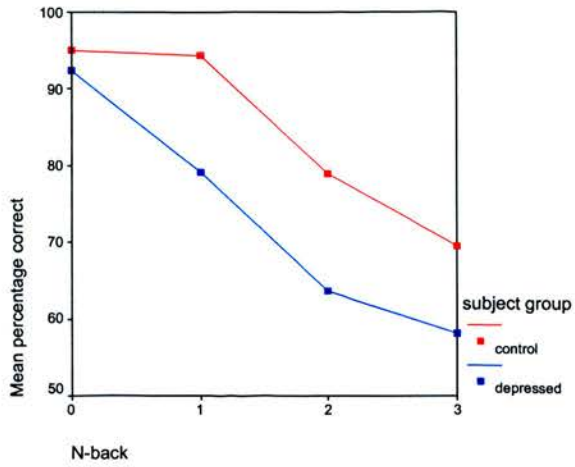

Figure 3.4: Mean percentage correct at each level of n-back in experiment one: 20 controls vs. 20 patients

In addition to the significant main effects outlined above, the data analysis also revealed a number of significant within-subjects contrasts. With regards to the level of difficulty of n-back significant reverse Helmert (or difference) contrasts were noted between 1- and 0-back (i.e. $F_{(1,38)} = 5.54$, $p = 0.024$), between 2- and 1-back (i.e. $F_{(1,38)} = 65.26$, $p < 0.001$), and between 3- and 2-back (i.e. $F_{(1,38)} = 53.90$, $p < 0.001$). The linear contrast for this factor was also significant, (i.e. $F_{(1,38)} = 56.78$, $p < 0.001$).

Furthermore, there was also a significant difference observed in the within-subjects reverse Helmert contrasts for the interaction between the level of n-back and participant group between the 1- and 0-back levels of the task (i.e. $F_{(1,38)} = 4.56$, $p = 0.039$). For this interaction effect all other contrasts failed to reach significance.

Therefore, based on the preliminary data analysis we can presume that both patients and controls experienced a linear increase in difficulty in performing the n-back task with each incremental increase in task difficulty, as reflected in the decrease in participant accuracy with the increase in N. It is also evident that patients perform consistently worse than controls across the task (i.e. see Figure 3.4), and that this difference is indeed significant. However, it would appear that this difference in accuracy on the n-back task between the participant groups is consistent in nature, i.e. patients do not appear to get disproportionately worse than controls as the level of the task difficulty increases.

3.3.2 Reaction time

The second 4 x 2 mixed ANOVA comparing the reaction time differences across the levels of task difficulty and between the subject groups also revealed a significant main effect of level of n-back (i.e. $F_{(1.934, 73.484)} = 15.34$, $p < 0.001$) and a significant main effect of participant group (i.e. $F_{(1,38)} = 25.16$, $p < 0.001$). Furthermore, there was an observed significant interaction between these two factors (i.e. $F_{(1.934, 73.484)} = 4.18$, $p < 0.02$).

The significant within-subjects contrasts observed in this analysis included significant quadratic and cubic contrasts for both level of n-back (i.e. $F_{(1,38)} = 6.81$, $p = 0.013$ and $F_{(1,38)} = 5.19$, $p = 0.028$) and for the interaction between level of n-back and participant group (i.e. $F_{(1,38)} = 4.40$, $p = 0.043$ and $F_{(1,38)} = 10.53$, $p = 0.002$). The linear contrast for level of n-back was also significant, (i.e. $F_{(1,38)} = 19.82$, $p < 0.001$).

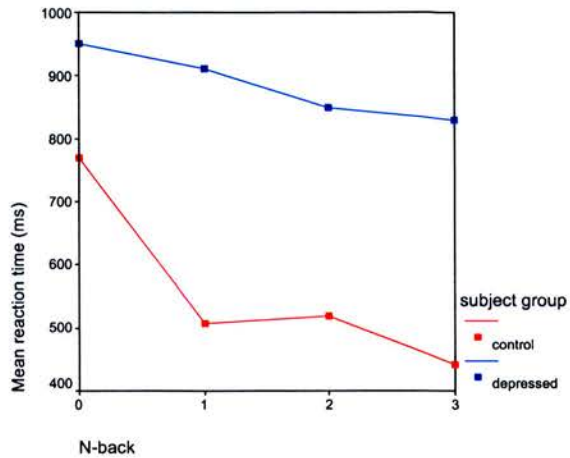

Figure 3.5: Mean reaction time (ms) at each level of n-back: Patients vs. controls

Post-hoc paired samples t-tests, using Bonferroni correction for multiple comparisons, revealed a significant difference in the mean reaction time across groups between 0- and 1-back levels of task difficulty (i.e. $t_{(39)} = 4.40$, $p < 0.001$). However, there was no significant difference observed between 1- and 2-back task levels (i.e. $t_{(39)} = 1.06$, $p = 0.296$), nor between 2- and 3-back levels (i.e. $t_{(39)} = 1.64$, $p = 0.109$).

Moreover, post-hoc independent samples t-tests, again using the Bonferroni correction, revealed a significant difference between patients and controls at all levels of the n-back task

(i.e. 0-back $t_{(38)} = -2.93$, $p = 0.003$, 1-back $t_{(27.960)} = -5.42$, $p < 0.001$, 2-back $t_{(38)} = -4.49$, $p < 0.001$, 3-back $t_{(27.117)} = -3.99$, $p < 0.001$).

Based on this preliminary analysis of the data we may presume that patients are significantly slower than controls to respond to stimulus items at all levels of the task. As with the differences observed in accuracy, it would appear that this deficit is consistent in it's nature, in so much as the disparity in the reaction times of patients and controls does not appear to either increase nor decrease across the levels of the task.

Furthermore, it may be presumed that while the reaction times of both patients and controls decreases (i.e. they get faster) between the baseline level of the task (i.e. 0-back) and the subsequent task levels, there is no relative speeding up or slowing down between the 1-, 2-, and 3-back levels.

These findings support the idea of impairment in working memory function in the depressed patients, accompanied by significant psychomotor slowing in this group.

3.3.3 Controlling for demographic differences between participant groups

While attempts were made to match the depressed patients with controls of the same age, gender, and IQ, the resultant samples did differ significantly in their mean NART estimated IQs. More specifically, it was noted that the mean IQ of controls was greater than that of patients (i.e. $t_{(37.477)} = 2.46$, $p = 0.019$), despite a similar range of scores in each group (i.e. range for controls = 97 – 127, range for patients = 96 – 129). This was of some concern given previous observations of the relationship between specific measures of performance, such as tests of psychomotor function (e.g. inspection time) and measures of individual difference such as IQ (e.g. Deary & Stough, 1996; Deary, McCrimmon & Bradshaw, 1997). Therefore, in order to attempt to control for the effect of any difference in IQ between the patients and controls on the results noted above two mixed analyses of co-variance were carried out, i.e. one for accuracy and one for reaction time data. The same factors were entered into these analyses as were entered in the previous ANOVA calculations (i.e. level of difficulty of n-back and participant group). However, this time NART estimated IQ was included as a co-variate.

3.3.3.1 Accuracy

As opposed to the previous analysis of accuracy on the n-back task, there was no observed significant main effect of level of n-back when IQ was entered as a co-variate (i.e. $F_{(3,111)} = 1.97$, $p = 0.123$). However, there was still a significant main effect of participant group (i.e. $F_{(1,37)} = 6.856$, $p = 0.013$).

In addition, there were two significant interactions noted in this analysis. The first of these was the interaction between level of n-back and IQ (i.e. $F_{(3,111)} = 3.30$, $p = 0.023$). The interaction between level of n-back and participant group was also significant (i.e. $F_{(3,111)} = 2.70$, $p = 0.049$).

In order to determine at which levels of n-back participant IQ has a significant impact upon performance post-hoc correlations were carried out. It was found that NART estimated IQ was correlated significantly with performance at the 0-back level of the task (i.e. $r = 0.33$, $p = 0.039$). However, there was no significant correlation between IQ and performance at any other of the task levels. It should be noted, however, that if we were to correct for multiple comparisons this correlation would become non-significant.

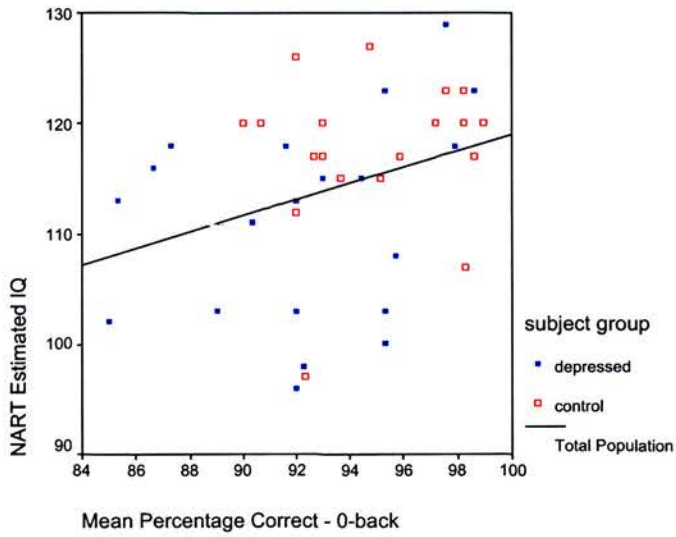

Figure 3.6: Scatterplot of participant's NART estimated IQ against the percentage of items correct at the 0-back level of the n-back task.

With regards to the within-subjects contrasts, a significant linear contrast was observed with regards to the interaction between participant IQ and level of n-back (i.e. $F_{(1,37)} = 4.12$, $p = 0.05$). All other within-subjects contrasts were non-significant.

Post-hoc independent samples t-tests revealed a significant difference between patients and controls on 0-back (i.e. $t_{(38)} = 2.39$, $p = 0.022$), 1-back (i.e. $t_{(20.787)} = 2.69$, $p = 0.007$), and 2-back (i.e. $t_{(33.47)} = 2.43$, $p = 0.01$) task levels, but not at the 3-back level (i.e. $t_{(38)} = 1.41$, $p = 0.084$). However, after adjusting the critical value of p in order to control for multiple comparisons, it was concluded that the only significant differences between patients and controls had occurred at the 1- and 2-back levels of the n-back task.

It can, therefore, be concluded that while performance, in terms of accuracy, does decline with increasing level of difficulty of n-back, this decline is not statistically significant when we control for participant IQ. Furthermore, it may be inferred that the effect of IQ on performance of the task may only be significant at the baseline level of the task.

Finally, we can conclude that not only do patients perform worse than controls on the n-back task; but that when IQ is controlled for there is an apparent increase in the effect of diagnosis. Moreover, it would appear that the differences observed between the experimental groups is underpinned by a significant difference in performance at the 1- and 2-back levels only.

3.3.3.2 Reaction Time

As with the accuracy analysis, when IQ was entered as a co-variate in the analysis, there was no significant main effect of n-back on participant reaction time (i.e. $F_{(3,111)} = 1.85$, $p = 0.142$). There was also no significant interaction between level of n-back and participant IQ (i.e. $F_{(3,111)} = 1.23$, $p = 0.303$). However, there was both a significant main effect of participant group (i.e. $F_{(1,37)} = 21.90$, $p < 0.001$) and a significant interaction between participant group and level of n-back (i.e. $F_{(3,111)} = 4.94$, $p = 0.003$).

In addition, while there were no significant within-subjects contrasts with regards to level of n-back or it's interaction with participant IQ, there were both linear and cubic contrasts for the interaction between level of n-back and participant group (i.e. $F_{(1,37)} = 4.54$, $p = 0.040$ and $F_{(1,37)} = 9.41$, $p = 0.004$, respectively).

In order to determine the nature of the interaction between participant group and level of n-back, post-hoc one-way within subjects ANCOVAs were carried out. Each of these analyses

estimated whether there was a significant difference between depressed patients and healthy controls at each level of n-back, after controlling for participant IQ. The results of these analyses were indicative of significant main effect of participant group at all levels of n-back (i.e. 0-back: $F_{(1,37)}= 5.79$, $p = 0.021$; 1-back: $F_{(1,37)}= 24.59$, $p < 0.001$; 2-back: $F_{(1,37)}= 18.29$, $p < 0.001$; and 3-back: $F_{(1,37)}= 15.91$, $p <0.001$). Thus, indicating that the interaction effect was due to differences in the magnitude of the discrepancy in performance of patients and controls and each level of the task, after controlling for IQ.

Therefore, we can conclude that not only does participant IQ have a significant effect on the effect of level of n-back with regards to accuracy but also significantly impacts any effect relating to mean reaction time. However, it would appear that any differences in the performance of patients and controls were not necessarily affected by the disparity in mean IQ between the groups. This is evident in both the consistency of the main effect of participant group and interaction between participant group and level of n-back across the two separate analyses.

3.4 Effect of clinical variables upon cognitive performance

As previously noted, some studies have highlighted the impact of clinical dimensions on participant outcome on measures of cognitive performance. For example, factors of interest highlighted in other studies have included aspects of illness such as severity of depression, and duration of illness, although there is considerable disparity regarding the importance of such factors on task performance. Therefore, further exploratory analyses (i.e. Pearson's product moment correlations) were carried out to examine the relationship between the clinical measures obtained in this study and the measures of cognitive performance (i.e. TEA subtests and n-back measures) in the patient sample.

Significant correlations were only observed between the length of time since initial diagnosis and mean percentage correct at the 2- and 3-back levels of the n-back task (i.e. $r = -0.51$, $p = 0.021$ and $r = -0.52$, $p = 0.020$, respectively) and between BDI score and mean percentage correct at the 3-back level only (i.e. $r = -0.56$, $p = 0.011$). Therefore, it appears that duration of illness and self-assessed severity of depression may have a possible effect upon performance but only at the more difficult levels of the task.

Chapter 4: Methodology - Experiment Two

4.1 Design

As with experiment one, a case control study with a single between subjects factor of participant group (i.e. depressed patients vs. healthy controls) and the within subjects factor of level of difficulty of n-back (i.e. 0-, 1-, 2-, and 3-back) was used to test the experimental hypotheses. In terms of behavioural performance, the dependent variables were mean percentage correct and mean reaction time, at each level of n-back, with both simple group and task difficulty effects and group x task difficulty interactions being of interest.

Participants' performance on the n-back task was assessed while undergoing a functional MRI scan, i.e. using BOLD-sensitive, echo planar imaging (EPI), with a parametric, block design. Therefore, the additional dependent variables in the present study were increases and decreases in regional brain activity with increasing task difficulty (i.e. in both patients and controls), and relative increases and decreases in functional activation between patients and controls associated with the linear increase in the level of difficulty of the n-back task.

4.2 Participants

4.2.1 Recruitment

The recruitment of participants for this study was covered by the same ethical and management approval as was obtained for the first study. This was due to the fact that a single submission was made to the appropriate ethics committees detailing both investigations, with the first study being noted as a pilot investigation and the second study as the main experiment.

4.2.1.1 Patient recruitment

A number of patients who participated in the first study also chose to participate in the functional MRI investigation. In order to recruit the additional participants required for the study the same prospective approach to patient recruitment that was used in the pilot study was employed (see Chapter 2 for full details).

In brief, staff at the Royal Edinburgh Hospital that were involved in care of patients were provided with the two information sheets (i.e. 'Information for Medical Staff' and 'Patient Information Sheet': see Appendix 2). They were asked to confer the participant information sheet upon any individuals in their care who they felt would be suitable to take part in the

study and who would be able to take part. Staff were also asked to provide details of those patients who were interested in participation to the researchers. Moreover, they were asked to provide details of other salient information about the patient, e.g. if there was any known history of drug or alcohol abuse.

This approach to patient recruitment was supplemented by regular visits and telephone calls to the hospital wards and day hospitals to check on recent admissions and status of patients who were likely to suitable for participation.

Once suitable individuals had been identified they were contacted directly by the researchers. The full outline of the aims and methods of the study were then explained to the individual in question, and they were given the opportunity to ask any questions they had regarding the investigation. Patients were given a minimum of 24 hours to consider participation, during which they were advised to discuss participation with their friends and family, as well as those responsible for their psychiatric care. If after careful consideration the patient was willing to participate in the study arrangements were made for pre-testing (if necessary) and scanning sessions, and their consultant was notified of the patient's intention to participate in the study.

4.2.1.2 Control recruitment

As with the patient participants, some of the control participants in experiment two had also participated in the pilot study. The remaining control participants were recruited opportunistically. Potential controls were approached based on either an expressed interest in participation in the study or through recommendation from colleagues, and were selected based on their ability to fulfil the criteria used to match controls to patients (see Chapter 2: Methodology: Experiment One). Individuals who were willing to consider participation as a control participant were given a copy of the information sheet for participants, and asked to take a minimum of 24 hours to consider participation. It was also recommended that they discuss participation in the study with their friends and family.

While the control sample included staff of the University of Edinburgh, Division of Psychiatry and the Royal Edinburgh Hospital, it was ensured that all individuals were

aware that participation was entirely voluntary and that no control participant was involved in a dependent relationship with any of the researchers.

4.2.2 Participant details

Participants were ten individuals with a diagnosis of major depressive disorder and ten matched normal, healthy controls. Patients and controls were matched as closely as possible for age, gender, and IQ (see Table 4.1). Where possible they were also matched as closely as possible for occupation. Within the patient sample there was one left-handed and nine right-handed participants. All of the control participants were right-handed.

Patients were either in- or out-patients (i.e. 3 and 7 respectively) of the Royal Edinburgh and associated hospitals. They were selected on the basis of a diagnosis of major depressive disorder (as confirmed by a member of staff involved in their psychiatric care) and a minimum score of 15 on both the BDI and HRSD at the time of testing.

Participant group	*Mean age (years) (mean(s.d.))*	*Mean IQ (mean(s.d.))*	*Male: Female*
Patients	31.9 (7.42)	107.2 (7.53)	2:8
Controls	30.6 (8.18)	112.1 (8.40)	3:7

Table 4.1: Summary of participant demographic details: Experiment Two

All participants were required to meet the same exclusion criteria as experiment one (see Chapter 2). However, in addition, given that participants were required to undergo magnetic resonance imaging, it was ensured that individuals met the following additional exclusion criteria: No history of head surgery; no metal fragments in any part of the body (e.g. shrapnel), either past or present; no previous injury incurred while working with metal which required medical attention; and no metal implants e.g. joint replacement, Harrington rods etc.

It was also noted whether participants wore dentures, a dental plate, a brace, contact lenses, a hearing aid, an intrauterine contraceptive device (IUCD) or sterilisation clips.

Within the depressed participant group nine patients were taking anti-depressant medication at the time of participation (see Table 4.2). One patient was taking a combination

of medications at the time of participation, i.e. tryptophan, trazodone, and diazepam. The single patient participant who was not medicated had been medication free for a period of 2 months prior to participation. This patient had previously been prescribed a course of venlafaxine.

Anti-depressant medication	*Class*	*Number of participants*
Clomipramine	Tricyclic	1
Imipramine	Tricyclic	1
Reboxitine	NARI	1
Trazodone	SSRI	1*
Tryptophan	Amino acid	1*
Venlafaxine	SSRI & NARI	5

Table 4.2: Antidepressant medication prescriptions of patient participants - Experiment two. (* = Same participant)

Eight patients and five controls that participated in the current experiment had previously taken part in the pilot study. As a result of this these individuals had already completed one full trial of the n-back task prior to scanning. For this reason all novel participants were given an opportunity to complete a practice session on the n-back task prior to scanning. It was felt that this was particularly advantageous with the patient sample as it ensured that patients were capable of undertaking the task. Accordingly, any patients likely to experience a catastrophic reaction to testing could be deselected prior to scanning.

4.2.3 Excluded/withdrawn participants

Three patients were recruited via the procedure outlined above but failed to score a minimum of 15 on the HRSD, and thus were excluded from any further testing. A further eight patients were approached by their consultant and agreed to participate in the study, but failed to respond to numerous attempts to contact them and arrange appointments for testing. In addition one patient experienced a catastrophic reaction to testing during the practice session, and was therefore excluded.

Furthermore, two volunteers who were initially selected to participate as matched controls were also excluded from the study. After recruitment it was discovered that one of these controls had suffered a number of mild head injuries in childhood, and had experienced a brief episode of depression during adolescence. The second of these two controls, while

having not been diagnosed with major depressive disorder, had previously been prescribed anti-depressant medication. Therefore, in order to preserve the integrity of the control sample it was deemed appropriate to not include either of these individuals.

4.3 Materials (see Appendix 2)

4.3.1 Pre-test materials

The same participant information sheet and consent form as were used in the first study were employed in the current investigation. Three additional pre-test measures were also employed in this study. The first of these was a medical questionnaire similar to the one employed in experiment one. However, in the version for this study, participants were also asked to indicate whether they were left or right handed.

The second measure completed by participants was a pre-scan questionnaire designed to ascertain whether, or not, there were any grounds for exclusion from MRI scanning (as per the additional exclusion criteria outlined above). For example, participants were asked to whether they had any metal objects or fragments in any part of their body.

The final pre-test measure was a patient information sheet. This form was constructed for use by a member of the staff involved in patient care for the provision of patient information relevant to participation in this study.

4.3.2 Affective indices

The affective assessments used in this study were the Beck Depression Inventory Beck et al., 1961, the Stress Arousal Checklist Mackay et al., 1978, the Alderley Park State Questionnaire Walker, 1990, and the Hamilton Rating Scale for Primary Depressive Illness Hamilton, 1967. An account of the nature of these assessments and a brief description of their administration can be seen in Chapter 2.

4.3.3 Cognitive assessments

National Adult Reading Test Nelson & Willison, 1991

The NART was employed in order to obtain an estimate of WAIS-R Full Scale IQ – i.e. current IQ in the controls and premorbid IQ in the patient sample.

The Test of Everyday Attention Robertson et al., 1994

The same subtests of the TEA that were used in the pilot study were used in the current investigation, i.e. the Elevator Counting with Distraction and Visual Elevator subtests.

The n-back task

The n-back task that we created was specifically designed in order to make it appropriate not only for neuropsychological testing but for use in functional imaging investigations. Therefore, we were able to utilise the same version of the n-back task as was employed in the first experiment in this study. The structure of the task was identical to the original version; however, the program for the paradigm was altered in order to make the task compliant with the software used to present stimuli in the scanner (i.e. Integrated Functional Imaging System (IFIS; Psychology Software Tools). This alteration simply involved editing the original E-prime programme file by including a number of IFIS extensions that allow the task to be synchronised with the scanner. The aim of this type of editing of the task is to ensure that the presentation of the behavioural paradigm will be appropriately co-ordinated with the acquisition of the functional imaging data.

Additional editing of the task focussed on the length of the paradigm. Given the relatively large number of repetitions of the levels of the n-back task employed (i.e. 10 blocks of each of 1-, 2-, and 3-back, and 30 blocks of 0-back) the original running time of the task was approximately 30 minutes. Therefore, it was decided that it would be advantageous to separate the original task into two distinct experimental blocks, each consisting of five trials of 1-, 2, and 3-back with each of these blocks being separated by a block of 0-back.

The final alteration that was made to the n-back task was the revision of the length of each individual block of n-back. In the original paradigm there were equal numbers of items in each n-back trial. Given that a block of 0-back preceded each block of 1-, 2-, and 3-back there was a considerably greater proportion of 0-back trials than any other single type of n-back trial. As we were more interested in the pattern of activation associated with the increased load on the central executive, rather than that associated with the baseline processes, it was decided that we should alter the number of 1-, 2-, and 3-back trials in order to increase the proportion of data acquired relating to these experimental manipulations. Therefore, 1-, 2-, and 3-back trials were extended to include the presentation of 14 stimulus items within each

block. Accordingly, the blocks of 0-back were reduced to the presentation of 9 stimulus items.

4.3.4 Scanner specifications and scanning protocol

All participants were scanned in a 1.5 T GE Signa MRI scanner, which was located at the SHEFC Brain Imaging Research Centre, at the Western General Hospital, Edinburgh. BOLD sensitive echo planar fMRI images were acquired with a TR of 2.5 seconds, and a TE of 40 milliseconds. The flip angle was 90º, with a field of view of 24 cm. The in plane resolution was 64 x 64, with a plane orientation that was near axial (i.e. aligned in parallel with the anterior commisure-posterior commisure (AC-PC) line). All functional scans were 5mm in thickness with no slice gap, thus a total of 30 slices were obtained. Data was acquired for two functional sessions, with each functional acquisition being 18 minutes 55 seconds in length (see details below). T2 and T1 weighted structural images were also obtained for each participant. The scanning parameters for these acquisitions were as follows:

	T1 weighted structural image acquisition	*T2 weighted structural image acquisition*
TE (milliseconds)	Min full	102
TR (milliseconds)	-	6300
TI (milliseconds)	600	-
Flip angle	15	-
Field of View	22	24
Matrix	256 x 192	256 x 256
Slice thickness (mm) / No. of slices	1.7/128	5/20
Slice Gap (mm)	0	1.5
Time (mins)	7 min 15 sec	1 min 41 sec

Table 4.3: Technical parameters for T1 and T2 weighted structural image acquisitions – Experiment two.

4.4 Procedure

4.4.1 Pre-test measures

As in the original study, participants were provided with the information sheet a minimum of 24 hours prior to participation, and were given the opportunity to pose any queries that they had about the nature of the study to the researchers. They were also advised to consult medical staff (where applicable) and their friends and family regarding participation.

Participants were asked to sign three copies of the consent form, one copy for their own records, one for the researchers, and, in the case of patients who participated, one copy to be appended to their medical records. Furthermore, all participants were asked to complete two pre-test questionnaires, i.e. the medical questionnaire and a pre-scan questionnaire, as previously outlined.

4.4.2 Affective assessment

All affective indices were completed on the day of participation, prior to the commencement of scanning. All participants completed the BDI Beck et al., 1961, the SAC Mackay et al., 1978, and the APSAQ Walker, 1990 prior to commencing scanning. Patients were additionally required to complete the HRSD Hamilton, 1967.

In addition, for each patient who participated, an individual involved in patients' psychiatric care was asked to complete a patient information sheet. As in experiment one, this form was used to corroborate information the patient had provided regarding their medical background and to acquire any additional information which may have been of interest to the researchers, e.g. current medication (including dosage), length of depressive illness etc.

4.4.3 Cognitive assessment

Prior to scanning, all participants completed the two TEA subtests Robertson et al., 1994. Participants who had not previously participated in the first experiment also completed the NART Nelson & Willison, 1991 and the original version of the n-back task (see Chapter 2 for details). This latter assessment was done in order to match participants who only participated in the second study with those who had participated in both studies in terms of level of practice on the n-back task.

4.4.4 Functional magnetic resonance imaging

4.4.4.1 Paradigm presentation

In functional MRI there are two typical strategies used for the presentation of behavioural paradigms, i.e. block-design and event-related. Block-design presentation involves determining the changes in cerebral activation during performance over the extended period of a block of a particular task. Event-related presentation, on the other hand, is concerned

with measuring the level of activation across the cortex (or in regions of interest) at a discrete time point that corresponds to the presentation of a specific stimulus or a specific response. While event-related presentation can result in reduced motion artefacts and practice effects, block-design does have the advantage of being a relatively simple and robust approach to activation studies, and can give researchers a better signal to noise ratio. Therefore, the current study decided to take an initial block-design approach to the presentation of the n-back task. However, the design of our original paradigm also allowed for the potential analysis of event-related responses at a later date if necessary.

The n-back task was presented visually to participants in the scanner using a LCD display mounted on the head coil (IFIS: Psychology Software Tools, Pittsburgh, PA). Once the participant's comfort in the scanner had been assured it was determined whether or not they could adequately read information presented on this display. Prior to the practice phase participants viewed a number of instructions screens, which outlined the nature of the task in general and the nature of each of the various levels of n-back. They were instructed to respond using the pushbutton units (IFIS: Psychology Software Tools, Pittsburgh, PA). Each unit is ergonomically-shaped, with a pushbutton beneath the thumb and each fingertip. Each participant was provided with a right-hand pushbutton unit and was advised that, in terms of responding, the fingers of the right hand should be considered as relating to positions 1 – 5 moving from left to right, from the thumb (i.e. position 1).

For the purposes of scanning there were three n-back phases, i.e. an initial practice phase, followed by two experimental phases. Although all participants had completed an entire run of the n-back task it was felt that a practice within the scanner would be advantageous as it would give each individual the opportunity to get used to both the type of display and the response units. In this practice phase participants were given the opportunity to attempt a block each of 1-, 2-, and 3-back, with each block being separated by a block of 0-back. In the experimental trials participants completed five blocks each of 1-, 2-, and 3-back, again with a block of 0-back occurring between each (i.e. resulting in a total of 15 blocks of 0-back).

As a result of the changes made to the experimental paradigm there was a notable change to the total run time of the n-back task. Each stimulus item was presented with an ISI of 3 seconds. Given that there was 9 items in each 0-back block and 14 items in all other n-back

blocks, the length of each 0-back block was 27 seconds, with all other n-back blocks having a total length of 52 seconds Furthermore, between each n-back block a prompt screen, indicating which task (i.e. 0-, 1-, 2-, or 3-back) the participant was to perform appeared for 3 seconds. The resultant length of the practice phase was, therefore, 6 minutes and 15 seconds, with each of the two experimental phases having a run time of 18 minutes and 55 seconds (see Figure 4.1).

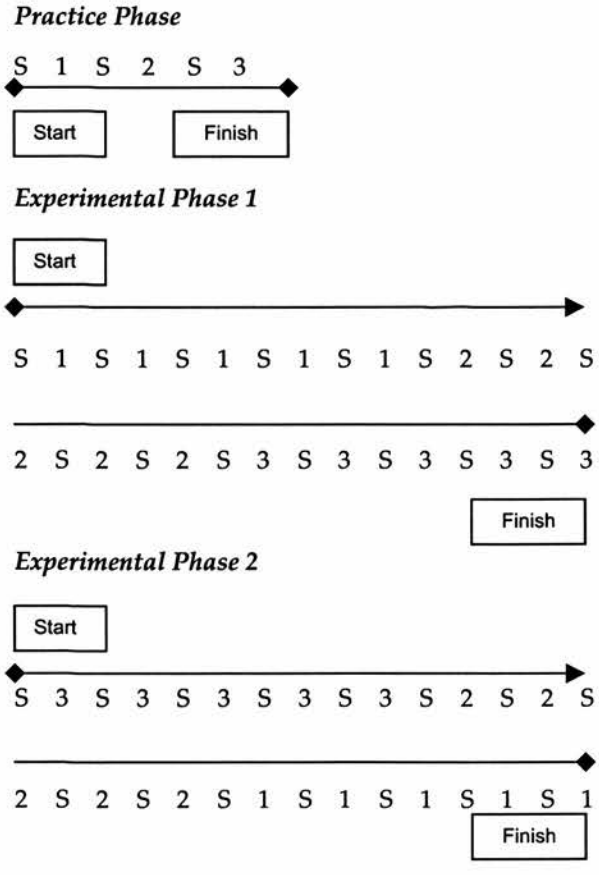

Figure 4.1: Running order for presentation of n-back blocks in each phase of the n-back task during functional imaging – Experiment two. Note: S = shadow, 1=1-back, 2=2-back, and 3=3-back.

A functional pre-scan and the T2 weighted structural scan were acquired during performance of the practice phase. Participants then attempted the first experimental phase, which was followed by the T1 weighted structural scan. Following this scan the second functional pre-scan was conducted. On completion of this scan participants attempted the second experimental phase.

As previously noted, participants performance on each of the n-back trials was recorded in terms of accuracy (i.e. correct or incorrect) and reaction time (in milliseconds).

4.4.5 Data Analysis

Full details of all analyses (behavioural and functional) can be seen in the following chapter (i.e. Chapter 5: Results: Experiment Two).

4.4.5.1 Behavioural Data

The behavioural data were analysed using SPSS for Windows (Release 11; SPSS Inc.). The main analyses were two 4 x 2 x 2 mixed ANOVA's, considering the effect of level of n-back task difficulty (i.e. 0-, 1-, 2-, or 3-back), participant group (i.e. patients vs. control), and imaging session (i.e. experimental phase 1 vs. experimental phase 2), on both accuracy (i.e. mean percentage correct) and reaction time. In addition, independent samples t-tests were conducted to compare patients and controls on each of the other measures obtained during the study.

4.4.5.2 Imaging Data

Functional imaging

All functional data were processed and analysed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm), running in MATLAB (Mathworks, Natick, MA, USA).

- Data preprocessing

Prior to preprocessing, participants BOLD EPI images were reconstructed to ANALYSE format (Mayo Foundation, Rochester, MN, USA). For each participant, EPI volumes were then realigned to the first volume in the series using rigid body transformation. Following realignment the movement parameters for each participant were examined in order to determine the degree of movement of participants in the scanner, during functional imaging.

The functional imaging data were then normalised. Given the noted occurrence of lesions in the temporal cortex in two of the depressed patients (see section 5.6 for details), prior to normalisation each participant's EPI images were co-registered to their own T1 structural image. The functional images were normalised using a linear affine transformation followed by non-linear deformations, and were resampled using sinc interpolation to cubic voxels of size $8mm^3$ (i.e. 2 x 2 x 2 mm).

The normalised images were then smoothed spatially, in order to minimize residual inter-participant differences, using a 3D Gaussian filter (i.e. 6 x 6 x 6 mm^3 FWHM (full width half maximum)).

- Data analysis

Fixed effects analyses were initially calculated to determine linear increases and decreases in activation in individual voxels with increasing task difficulty, using a block design, for patients and controls. In addition, fixed effects analyses were then conducted in order to compare patients and controls in terms of relative differences in increased and decreased activation associated with increasing task difficulty.

Second level (i.e. 'random effects') analyses were then conducted in order to account for the influence of individual variability on the observed pattern of activation. These analyses were based upon the outcomes of the fixed effects contrasts for each individual participant. As with the fixed effects, random effects were calculated for the voxels of increased and decreased activation in controls and patients, associated with the linear increase in difficulty of n-back, and for the relative differences in activation between patients and controls.

As a result of some of the behavioural observations (see Chapter 5) it was decided that we should consider the pattern of activation associated with correct responses only in patients and controls. Therefore, a series of event-related analyses were conducted. Instances where both patients and controls performed accurately were isolated and analysed for changes in activation at each level of task difficulty and associated with the linear increase in n-back difficulty. In addition the data was also analysed for relative differences in activation associated with correct responses only between the patients and controls. Moreover, comparisons were made between instances where patients performed the task correctly and when they performed the task incorrectly, at each level of n-back. Again, both fixed and random effects models were calculated.

Structural data

The T1 weighted structural images from each participant were examined for any evidence of structural deficit.

Chapter 5: Results - Experiment Two

Analysis of T1 weighted structural images revealed structural anomalies in three participants in the patient sample (see imaging results below for details). Detailed analysis of these apparent structural deficits revealed that in two of the three patients the anomalies in regions of cortex that were not involved in, or significantly close to, the average pattern of activation seen in the patient group during performance of the n-back task. Therefore, these individuals were included in the functional imaging analysis. The structural deficit in the third patient was determined to be in a region that was proximate to areas of functional interest. Accordingly, this patient was excluded from the analysis of functional imaging data.

In addition, a functional artefact was observed in the temporal lobes of one control participant (see imaging results below for details). Although there was no structural deficit associated with this dysfunction (as determined by examination of the T1 weighted structural image for this participant), there was a significant artefact on the EPI images obtained for the individual concerned. Consequently, this participant was also excluded from the analysis of functional images.

Therefore, the sample size for patients and controls was reduced to 9 for both groups in the functional imaging analysis. However, given that all participants met the criteria for participation, it was assumed that the behavioural data collected from all individuals during functional data acquisition was still valid with respect to behavioural and neuropsychological observations. Therefore, two behavioural analyses were conducted, i.e. an initial analysis including all participants involved in scanning and a secondary analysis involving only those participants whose data was included in the analysis of functional imaging.

5.1 Behavioural Results: All Participants

5.1.1 Affective indices

Independent samples t-tests revealed significant differences between the patients and controls on the BDI (i.e. $t_{(9.07)} = 6.43$, $p < 0.0005$), on the stress and arousal dimensions of the SAC (i.e. $t_{(9.77)} = 4.02$, $p = 0.0015$ and $t_{(18)} = 4.51$, $p < 0.0005$, respectively), and on the APSAQ (i.e. $t_{(10.75)} = 3.81$, $p = 0.0015$).

	Patients		*Controls*		*Mean Difference*
	Mean (s.d.)	Min-Max	Mean (s.d.)	Min-Max	
HRSD	21.10 (5.55)	15 – 32	N/A	N/A	N/A
BDI	28.00 (13.44)	10 – 51	0.60 (0.89)	0 – 2	27.40
SAC – Stress	9.70 (6.12)	1 – 17	1.10 (1.37)	0 – 4	8.60
SAC – Arousal	8.60 (3.59)	3 – 12	2.50 (2.32)	0 – 5	6.10
APSAQ	34.30 (12.99)	20 – 58	17.90 (4.07)	12 - 27	16.40

Table 5.1: Mean scores on each of the affective assessments in experiment two: Patients vs. controls

However, as with the previous study, the distribution of scores on each of the affective measures deviated significantly from a normal distribution (i.e. BDI S-W $_{(20)}$ = 0.82, p = 0.002; SAC-stress S-W $_{(20)}$ = 0.76, p < 0.001; SAC-arousal S-W $_{(20)}$ = 0.90, p = 0.042; and APSAQ S-W $_{(20)}$ = 0.85, p = 0.006). Therefore, the scores on each assessment were further compared using a series of Mann-Whitney U tests.

The non-parametric analyses also revealed a significant difference between the experimental groups on the BDI (i.e. U = 0.00, p < 0.001), on the stress and arousal indices of the SAC (i.e. U = 9.50, p = 0.001 and U = 10.00, p = 0.002), and on the APSAQ (i.e. U = 4.00, p < 0.001).

Therefore, it can be concluded that not only did the patients exhibit a significant level of depression in comparison to the controls, but they also experienced significantly higher levels of state stress, arousal, and anxiety at the time of testing.

5.1.2 Test of Everyday Attention

5.1.2.1 Elevator Counting with distraction

Independent samples t-test analysis of the elevator counting with distraction data revealed no significant difference between the experimental groups in the average number of correct responses. This was true for both the raw scores (i.e. t $_{(18)}$ = 0.00, p = 1.00) and the scaled scores (i.e. t $_{(18)}$ = -0.45, p = 0.329).

5.1.2.2 Visual Elevator

Independent samples t-tests were also used to compare patient and control performance on the visual elevator task (i.e. accuracy and reaction time).

5.1.2.2.1 Accuracy

While there was a significant difference between patients and controls on the raw accuracy scores (i.e. $t_{(18)} = -1.95$, $p = 0.034$) the scaled scores of the two experimental groups on the accuracy measure of the visual elevator task were not significantly different (i.e. $t_{(18)} = -1.47$, $p = 0.079$).

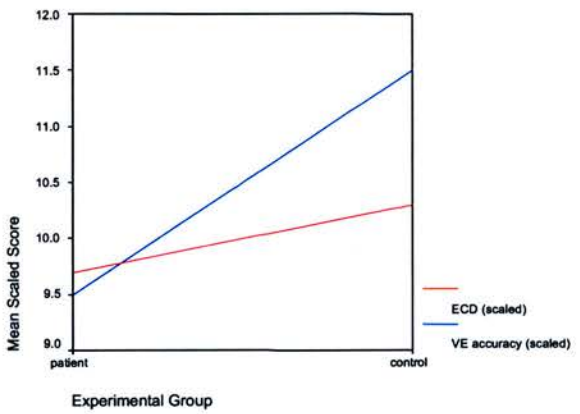

Figure 5.1: Comparison of mean scaled scores for accuracy on the elevator counting with distraction and visual elevator subtests of the TE – Experiment two (10 patients vs. 10 controls).

5.1.2.2.2 Timing

The t-test analyses also revealed a significant difference between patients and controls with respect to the average time taken per attentional switch on the visual elevator subtest. The experimental groups differed in both the mean raw scores (i.e. $t_{(9.68)} = 2.24$, $p = 0.025$) and the mean scaled scores (i.e. $t_{(11.83)} = -2.408$, $p = 0.017$) on this measure.

Therefore, it can be concluded that there was no evidence of a dysfunction of selective attention, cognitive flexibility, or auditory-verbal working memory in the patient group (as compared with healthy controls) in this study. However, the significant differences between patients and controls on the timing measure of the visual elevator task is indicative of psychomotor slowing associated with the experience of major depression.

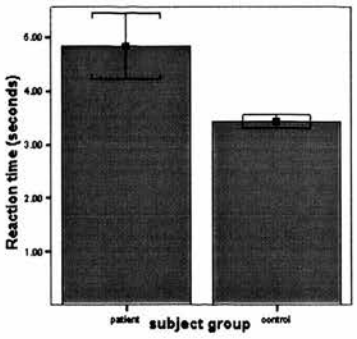

Figure 5.2: Mean time (seconds) per attentional swtich on each correct item of he VE task - Experiment two (10 pattients vs. 10 conrols)

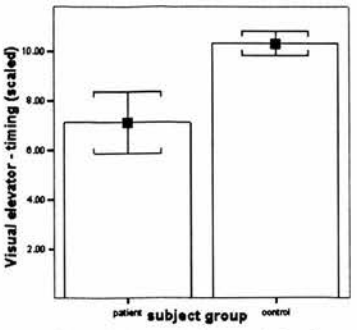

Figure 5.3: Mean scaled score on the visual elevator task - Experiment two (10 patients vs. 10 controls)

5.1.3 n-back task

The performance of participants on the task, as undertaken during functional imaging, was analysed using two 2 x 2 x 4 mixed ANOVAs, i.e. one for accuracy and one for reaction time. The main factors of interest were participant group (i.e. patients vs. controls) and level of difficulty of n-back. Although the effect of scanning session (i.e. session 1 vs. session 2) was not considered as an important factor in the formation of the experimental hypotheses for this study, it was included as a factor in the analyses in order to determine whether there was any significant effect on performance on the n-back task associated with the use of two different behavioural sessions during scanning.

5.1.3.1 Accuracy

As in the previous experiment, accuracy was measured in terms of the percentage of correct responses at each level of n-back. The first ANOVA analysis revealed a significant main effect of level of n-back (i.e. $F_{(1.81,54)} = 17.15$, $p < 0.001$) and a significant main effect of group (i.e. $F_{(1,18)} = 4.727$, $p = 0.043$). However, there was no significant main effect of scanning session (i.e. $F_{(1,18)} = 0.37$, $p = 0.552$) and no significant interactions between any of the factors (i.e. n-back*Group: $F_{(1.81,54)} = 0.757$, $p = 0.465$; Session*Group: $F_{(1,18)} = 2.96$, $p = 0.552$; n-back*Session: $F_{(1.56,54)} = 1.855$, $p = 0.181$; n-back*Session*Group: $F_{(1.56,54)} = 0.237$, $p = 0.735$).

A priori reverse Helmert contrasts revealed a significant difference in average percentage correct between 2- and 1-back conditions (i.e. $F_{(1,18)} = 15.169$, $p = 0.001$) and between 3- and 2-back conditions (i.e. $F_{(1,18)} = 22.733$, $p < 0.001$). In addition, the linear contrast for level of n-back was also significant (i.e. $F_{(1,18)} = 24.135$, $p < 0.001$). However, the contrast between 1- and 2-back conditions (i.e. $F_{(1,18)} = 3.280$, $p = 0.087$) was not significant.

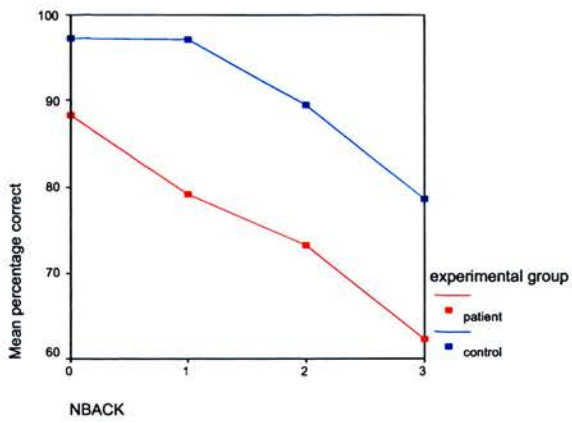

Figure 5.4: Mean percentage correct at each level of n-back – Experiment two (10 patients vs. 10 controls).

Post-hoc paired samples t-tests comparing the mean performance at each level of n-back revealed significant differences between 0- and 1-back (i.e. $t_{(19)} = 1.92$, $p = 0.035$), between 1- and 2-back (i.e. $t_{(19)} = 3.88$, $p < 0.001$) and between 2- and 3-back (i.e. $t_{(19)} = 3.76$, $p < 0.001$). These findings were still statistically significant after correction for multiple comparisons (i.e. Bonferroni).

Therefore, as predicted, both patients and controls exhibited a linear increase in difficulty associated with the linear increase in the level of n-back. Moreover, patients experienced greater difficulty across all levels of the task than control participants. As in experiment one, the impairment seen in patients was consistent in nature.

5.1.3.2 Reaction time

The results of the second mixed ANOVA analysis revealed a significant main effect of n-back (i.e. $F_{(1.54,54)} = 19.04$, $p < 0.001$), a significant main effect of scanning session (i.e. $F_{(1,18)} = 8.21$, $p = 0.01$), and a significant interaction between level of n-back and scanning session (i.e. $F_{(3,54)} = 4.27$, $p = 0.009$) on the mean reaction time of participants. There was, however, no significant main effect of participant group (i.e. $F_{(1,18)} = 1.86$, $p = 0.190$), no significant interaction between scanning session and participant group (i.e. $F_{(1,18)} = 2.51$, $p = 0.131$), and no significant three-way interaction between level of n-back, scanning session, and participant group (i.e. $F_{(3,54)} = 2.20$, $p = 0.009$).

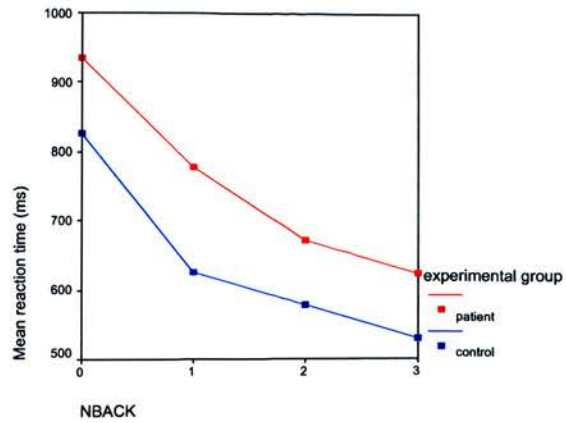

Figure 5.5: Mean reaction time (ms) at each level of n-back – Experiment two (10 patients vs. 10 controls).

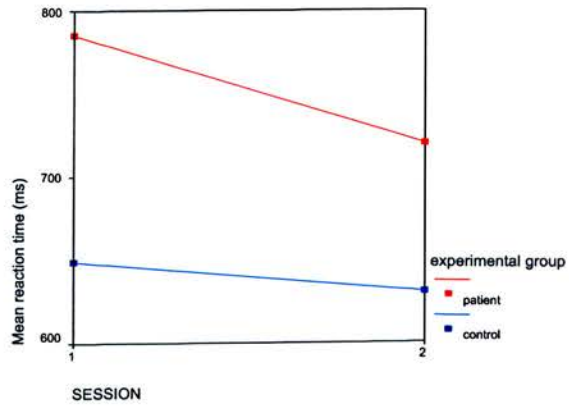

Figure 5.6: Mean reaction time (ms) for scanning sessions 1 and 2 – Experiment two (10 patients vs. 10 controls).

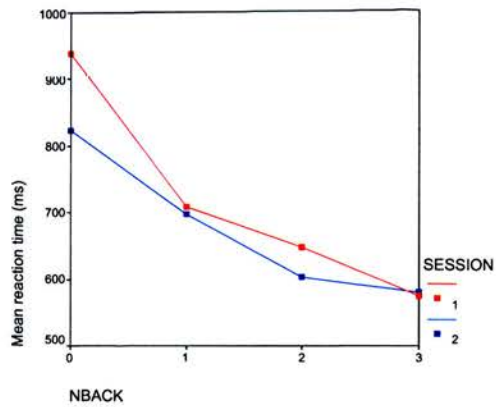

Figure 5.7: Mean reaction time (ms) at each level of n-back – Experiment two (Session 1 vs. session 2: all participants).

A priori reverse Helmert contrasts for level of difficulty of n-back revealed a significant difference in average reaction time between 1- and 0-back (i.e. $F_{(1,18)} = 14.80$, $p = 0.001$),

between 2- and 1-back (i.e. $F_{(1,18)} = 23.70$, $p < 0.001$), and between 3- and 2-back (i.e. $F_{(1,18)} = 20.01$, $p < 0.001$).

Post-hoc paired sample t-tests, with Bonferroni correction for multiple comparisons, revealed a significant difference in mean reaction time at the 0-back level between sessions 1 and 2 (i.e. $t_{(19)} = 6.603$, $p < 0.001$). However, no significant differences were observed between scanning sessions for 1-, 2-, and 3-back levels (i.e. $t_{(19)} = 0.409$, $p = 0.687$, $t_{(19)} = 1.398$, $p = 0.178$, $t_{(19)} = -0.150$, $p = 0.882$, respectively).

Further post-hoc analysis (i.e. paired samples t-tests, with Bonferroni correction) demonstrated significant differences in the mean reaction times at 0- and 1-back (i.e. $t_{(19)} = 3.737$, $p = 0.001$), between 1- and 2-back (i.e. $t_{(19)} = 3.303$, $p = 0.002$), but not between 2- and 3-back (i.e. $t_{(19)} = 2.004$, $p = 0.06$).

Thus, it may be asserted that, for all participants, RT was significantly inversely related to the increase in 'N' between the 0- and 2-back levels of the n-back task. However, participants did not experience any significant change in the time taken to respond to stimulus items with the change in task level to 3-back.

In addition, whereas participants average reaction times to 0-back items was significantly slower in the first scanning session, reaction times at the other levels of n-back were not significantly different between sessions.

It should also be noted that, in contrast to the results of experiment one, there was no significant difference in the reaction times of patients and controls during performance of the n-back task. This finding is indicative of relatively preserved psychomotor function in the group of depressed patients who participated in this study.

5.1.4 Relationship between clinical dimensions and cognitive performance: All participants

In order to determine whether there was any significant relationship between the affective states of the patients involved in this study and the measures of cognition employed a series of bivariate correlations were calculated (i.e. Pearson's product moment correlation co-

efficient). The results of these analyses revealed no statistically significant association between BDI, HRSD, SAC, and APSAQ scores for the depressed patients and their scores on both the subtests of the TEA and both accuracy and reaction time measures on the n-back task (i.e. $p_{(crit.)} \leq 0.05$).

5.2 Behavioural Results: Scanning analysis participants only

5.2.1 Participant details

Data obtained from 9 patients and 9 control participants was included in the final analysis of functional images (see Table 5.2 below).

Participant group	*Mean age (years) (mean (s.d.))*	*Mean IQ (mean (s.d.))*	*Male: Female*
Patients	32.00 (7.86)	108.22 (7.21)	2:7
Controls	31.33 (8.32)	112.56 (8.78)	3:6

Table 5.2: Demographic details of those participants included in the analysis of functional imaging data in Experiment Two.

Independent samples t-tests revealed no significant difference between these subgroups of patients and controls with respect to mean age or IQ (i.e. $t_{(16)} = 0.18$, $p = 0.863$ and $t_{(16)} = -1.5$, $p = 0.269$, respectively). Moreover, there was no significant difference in the distribution of male and female participants between the groups (i.e. $\chi^2_{(1)} = 0.599$, $p > 0.05$).

5.2.2 Affective Indices

The outcome of independent samples t-tests, used to compare the participant subgroups on the affective measures, were indicative of significant differences between patients and controls on the BDI (i.e. $t_{(8.06)} = 5.91$, $p < 0.001$), both the stress and arousal dimensions of the SAC (i.e. $t_{(8.66)} = 3.56$, $p = 0.003$, $t_{(16)} = 4.09$, $p < 0.001$, respectively), and on the APSAQ (i.e. $t_{(9.54)} = 3.44$, $p < 0.004$).

All of these measures, with the exception of SAC-arousal, deviated significantly from a normal distribution (i.e. BDI: S-W $_{(18)} = 0.81$, $p = 0.002$; SAC-stress: S-W $_{(18)} = 0.74$, $p < 0.001$; and APSAQ: S-W $_{(18)} = 0.84$, $p = 0.006$). However, Mann-Whitney U analyses confirmed the significant group differences on the affective indices (i.e. BDI: $U = 0.00$, $p < 0.001$; SAC-stress: $U = 7.50$, $p = 0.002$; and APSAQ: $U = 4.00$, $p < 0.001$).

	Patients		*Controls*		*Mean Difference*
	Mean (s.d.)	Min-Max	Mean (s.d.)	Min-Max	
HRSD	20.56 (5.59)	15 – 32	N/A	N/A	N/A
BDI	28.56 (14.13)	10 – 51	0.67 (0.87)	0 – 2	27.89
SAC – Stress	9.44 (6.97)	1 – 17	1.00 (1.41)	0 – 4	8.44
SAC – Arousal	8.22 (3.60)	3 – 12	2.33 (2.40)	0 – 5	5.89
APSAQ	34.44 (13.78)	20 – 58	17.89 (4.31)	12 – 27	16.56

Table 5.3: Mean scores on each of the affective assessments in experiment two for those participants included in the analysis of functional brain images.

Therefore, the same profile of affective state at the time of assessment in the subgroups of participants included in the functional imaging analysis mimicked the pattern seen in the entire participant sample. Thus, suggesting the subgroup of participants who were included in imaging analysis were representative of the group as a whole.

5.2.3 Test of Everyday Attention

5.2.3.1 Elevator counting with distraction

Independent samples t-tests revealed no significant difference in the mean number of correct items on the elevator counting with distraction task between patients and controls. Again, this was accurate for both raw and scaled scores on this task (i.e. $t_{(16)} = 0.08$, $p = 0.468$ and $t_{(16)} = -0.23$, $p = 0.411$).

5.2.3.2 Visual Elevator

5.2.3.2.1 Accuracy

Within these sub-groups, patients did not perform significantly worse than controls in terms of number of correct responses (scaled) on the visual elevator subtest. This was evident in the results of independent samples t-tests of the raw (i.e. $t_{(16)} = -1.55$, $p = 0.07$) and scaled (i.e. $t_{(16)} = -1.05$, $p = 0.15$) scores on this measure.

5.2.3.2.2 Timing

Patients were significantly slower than controls in the average time taken to make an attentional switch. This disparity in psychomotor function was reflected in the differences between the mean reaction time per attentional switch (i.e. $t_{(8.61)} = 1.89$, $p = 0.046$) and in the mean scaled scores (i.e. $t_{(10.66)} = -1.94$, $p = 0.039$) of patients and controls.

5.2.4 n-back task

5.2.4.1 Accuracy

A 4 x 2 x 2 mixed ANOVA of the average accuracy, i.e. percentage of correct responses, revealed a significant main effect of level of difficulty of n-back (i.e. $F_{(1.73, 48)} = 15.87$, $p < 0.0001$), but there was no significant main effect of scanning session (i.e. $F_{(1,16)} = 0.15$, $p = 0.708$) or participant group (i.e. $F_{(1,16)} = 2.93$, $p = 0.106$). Furthermore, no significant interactions between any of the factors was observed, i.e. n-back*Group: $F_{(1.731,48)} = 0.54$, $p = 0.566$; Session*Group: $F_{(1,16)} = 2.17$, $p = 0.160$; n-back*Session: $F_{(1.550, 48)} = 1.34$, $p = 0.272$; n-back*Session*Group: $F_{(1.550,48)} = 0.76$, $p = 0.448$).

A priori, reverse Helmert contrasts revealed a significant difference in performance between 2- and 1-back levels (i.e. $F_{(1,16)} = 10.99$, $p = 0.004$), and between 3- and 2-back levels (i.e. $F_{(1,16)} = 22.79$, $p < 0.001$), but not between 0- and 1-back levels (i.e. $F_{(1,16)} = 2.14$, $p = 0.163$) of the n-back task.

Post-hoc paired samples t-tests were conducted to further explore the main effect of level of difficulty of n-back. After appropriate adjustment for multiple comparisons, significant differences were noted between the 1- and 2-back levels of the task (i.e. $t_{(17)} = 3.36$, $p = 0.004$) and between 2- and 3-back levels (i.e. $t_{(17)} = 4.27$, $p < 0.001$). However, there was no apparent significant difference in the mean accuracy between the 0- and 1-back task levels (i.e. $t_{(17)} = 0.06$, $p > 0.05$).

5.2.4.2 Reaction time

A 4 x 2 x 2 mixed ANOVA of mean reaction time (ms) revealed a significant main effect of level of difficulty of n-back (i.e. $F_{(1.42, 48)} = 15.56$, $p < 0.001$), a significant main effect of scanning session (i.e. $F_{(1,16)} = 5.35$, $p = 0.034$), and a significant interaction between level of difficulty of n-back and scanning session (i.e. $F_{(3,48)} = 5.19$, $p = 0.003$). There was, however, no significant main effect of participant group (i.e. $F_{(1,16)} = 0.94$, $p = 0.346$), no significant interaction between level of n-back and participant group (i.e. $F_{(1.42,48)} = 0.10$, $p = 0.843$), no significant interaction between scanning session and participant group (i.e. $F_{(1,16)} = 1.63$, $p = 0.220$), and no significant three-way interaction (i.e. $F_{(3,48)} = 1.89$, $p = 0.144$).

Planned comparisons for mean reaction time at each level of n-back revealed a significant difference between 1- and 0-back (i.e. $F_{(1,16)} = 13.68$, $p = 0.02$), between 2- and 1-back (i.e. $F_{(1,16)} = 19.35$, $p < 0.001$), and between 3- and 2-back (i.e. $F_{(1,16)} = 14.41$, $p = 0.002$).

Post-hoc paired samples t-tests, with Bonferroni correction for multiple comparisons (i.e. $p_{(crit.)} = 0.0125$), revealed a significant difference in mean reaction time between sessions 1 and 2 at the 0-back level of task difficulty (i.e. $t_{(17)} = 6.51$, $p < 0.001$). However, there was no significant difference between scanning sessions at 1-back (i.e. $t_{(17)} = 0.06$, $p = 0.955$), 2-back (i.e. $t_{(17)} = 0.64$, $p = 0.528$), or 3-back (i.e. $t_{(17)} = -0.20$, $p = 0.848$) levels of tasks difficulty.

5.2.5 Relationship between clinical dimensions and cognitive performance: Scanning participants only

In those patients who were included in the scanning analyses, no significant associations were found between the measures of affective state (i.e. BDI, HRSD, SAC, and APSAQ) and any of the measures of cognitive performance (i.e. both TEA subtests and both accuracy and reaction time measures on the n-back task).

5.3 Summary of Behavioural Findings

5.3.1 Affective Indices

Prior to commencement of testing it was assured that all patients were exhibiting a significant severity of depressive symptomology, and that all controls had no history of psychiatric illness or current symptoms of major depression. This distinction between the experimental groups was supported by the observed significant difference in the mean BDI scores of patients and controls. Patients also exhibited significantly greater levels of state stress and arousal (as assessed by the Stress Arousal Checklist) and state anxiety (as assessed by the APSAQ) prior to participation.

5.3.2 Test of Everyday Attention

Overall, the outcomes on the TEA subtests suggest an absence of impairment in selective attention, cognitive flexibility, nor auditory verbal working memory in the patient group, as compared with healthy controls. However, despite similar levels of performance accuracy between the experimental groups, patients were slower to respond to stimuli in the visual elevator task. This was evident in the analysis of reaction times in both analyses of behavioural data in the current study.

5.3.3 n-back task

5.3.3.1 Accuracy

A significant main effect of level of difficulty of n-back was observed in both of the behavioural analyses, with planned comparisons revealing a significant difference between each consecutive level of task difficulty. Therefore, it would appear that all participants experienced an increase in task difficulty with each incremental increase in cognitive load on the n-back task.

Moreover, analysis of the data for all participants revealed a significant main effect of participant group, with patient scores being significantly lower than those of control participants. While this significant finding was not replicated in the analysis of data from those participants included in scan analyses, the pattern of findings was similar. Therefore, the failure to obtain a significant finding in this latter analysis may be the result of reduced statistical power due to the small sample numbers.

Both behavioural analyses confirmed the lack of a significant difference in performance across functional MRI scanning session. Thus, suggesting no effect of scanning session on the observed level of participant accuracy on the n-back task.

5.3.3.2 Reaction time

Overall, the results relating to participant reaction time on the n-back task are indicative of a significant decrease in participant reaction time with increasing task difficulty, i.e. as N increased participants exhibited a relative speeding up of their response times.

Examination of the descriptive data would seem to indicate that patient's reaction times were on average slower than those of controls (i.e. across all levels of n-back and across sessions). However, both behavioural analyses were suggestive of no effect of participant group on mean reaction time. This lack of a significant difference between patients and controls is indicative of relatively preserved psychomotor function in the depressed patients who participated in this study.

While there was an apparent reduction in reaction time with each increase in the level of task difficulty between sessions 1 and 2, there appeared to be little difference in the reaction

time scores for 1-, 2-, and 3-back conditions across the two imaging sessions. The only significant effect of scanning session was the apparent difference in the average reaction time at 0-back between sessions 1 and 2.

5.3.4 Relationship between clinical dimensions and cognitive performance

The findings of both sets of correlation analyses failed to find a significant association between severity of depression (i.e. both BDI and HRSD), state stress, and state anxiety in the depressed patients and their level of performance on the cognitive measures. Not only was there no significant association between affective scores and accuracy on the cognitive tasks but there was also no apparent relationship between affective state of depressed individuals and measures of psychomotor function in this study.

5.4 Comparison of the effect size for experimental group differences in performance on the n-back task: Experiment One vs. Experiment Two.

It is possible that the relatively smaller number of participants in experiment two had a significant impact upon the relative level of statistical power in this study. A reduced power level is of concern given the relative differences in the observations of previous investigations of WM function in MDD, which may reflect the magnitude of this type of effect. Thus, it was deemed appropriated to compare the relative effect size of participant group effects on performance on the n-back task between the first two studies. These comparisons were conducted for both accuracy and reaction time in each study (i.e. using Cohen's d estimates of effect size; see Figures 5.8 and 5.9 below).

Comparison of the relative effect size differences in accuracy on the n-back task between patients and controls in the two studies revealed a greater effect of participant group across all levels of N in the second experiment. However, these differences appear to be rather minimal in magnitude, implying that the findings of the two studies with regards to the effect of participants group on n-back accuracy are comparable.

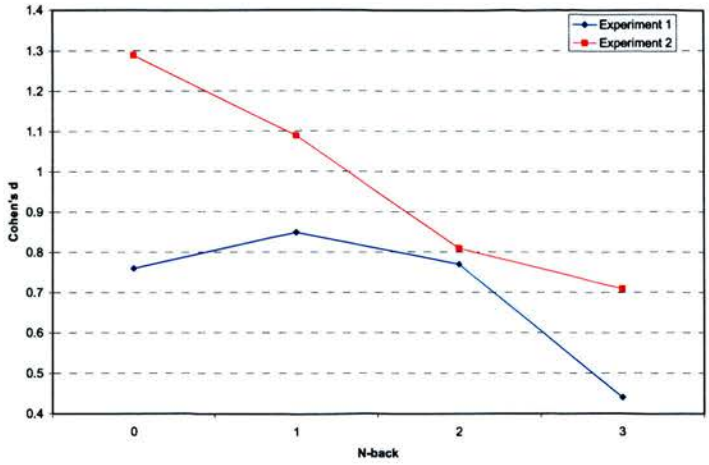

Figure 5.8: Comparison of effect size (i.e. Cohen's d) for the main effect of participant group on accuracy - Experiment one vs. experiment two

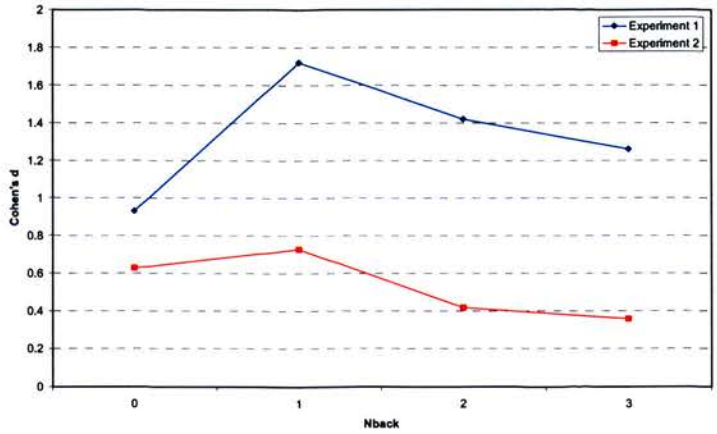

Figure 5.9: Comparison of effect size (i.e. Cohen's d) for the main effect of participant group on reaction time - Experiment one vs. experiment two.

In contrast to the effect of participant group on accuracy, the effect size with respect to the effect of experimental group on participant reaction time appears to be greater in the first experiment. Indeed, this may reflect the statistically significant effect of participant group on this measure that was noted in the first study, but not the second.

Overall, the pattern of results observed, in terms of effect size, is similar in the two studies. This may be indicative of reduced statistical power in the second study as a result of the smaller participant numbers. Alternatively, the differences between experimental conditions may be the result of a confounding effect of performance of the task during scanning in the latter experiment. Nonetheless, the similarities between studies are indicative of a consistent

profile of performance on the n-back task, between patients and controls, irrespective of experimental condition (i.e. experiment one vs. experiment two).

5.5 Structural imaging results

5.5.1 Patients

Examination of the structural images (i.e. T1-weighted MRI) revealed structural abnormalities in three of the patients. In two of these patients there were lesions in the temporal lobes, presumed to be small cerebral haemangioma – possibly the result of a minor head injury. Analysis of the patterns of functional activation associated with these two patients were determined not to differ significantly from that seen in the other depressed patients involved in the study. Moreover, the lesion sites in these individuals were deemed to be far enough removed from the regions of task associated activation. Therefore, both of these participants were included in the functional imaging analysis.

The third patient was noted to have a significant white matter lesion. When the pattern of activation during task performance was examined for this individual it was concluded that the lesion site was too close to regions of significant activation. More specifically, the lesion site was particularly close to posterior cortical regions that showed an apparent decrease in activation associated with the linear increase in task difficulty. Therefore, in order to minimise any distortion in the results of the functional imaging analysis this patient was excluded from the data analysis.

5.5.2 Controls

Analysis of the T1 images of the control participants revealed no significant abnormalities in cortical structure of any of the normal individuals who participated in this study.

5.6 Functional Imaging Results: Block design

Despite normal structural data in all of the control participants, during functional scanning of one participant there was a significant artefact in the functional images. It was suggested that the artefact might have been the result of a non-clinically significant abnormality in metabolic functions. As a result of the location (i.e. left temporal lobe) and extent of this artefact, this patient was also excluded from the analysis.

Consequently, this functional artefact and the noted significant structural abnormality in the patients meant that suitable imaging data was obtained from 9 depressed patients and 9 normal controls. Imaging data from these participants was examined for significant effects of the between groups factor of participant group and the within subjects factor of task difficulty upon cortical activation.

As previously outlined, all of the data were preprocessed and analysed using SPM99 (www.fil.ion.ucl.ac.uk/spm). For each individual participant BOLD EPI images were co-registered to their own T1 MRI image. Following co-registration the images were normalised and smoothed (i.e. see pp 132-133 for full details of the data preprocessing).

Fixed effects contrasts were then calculated for individual participants. Similar contrasts were also calculated for the relevant within- and between-groups factors. This first level analysis involved calculating the voxels in which activation was either increased or decreased in association with the parametric increase in the level of difficulty of the n-back task.

The fixed effects contrasts for each participant were then used to calculate within and between group random effects for factors of interest. Independent samples t-test were used to calculate within group contrasts, whereas between group contrasts were calculated using a one-way ANOVA.

In addition to these core analyses, contrasts were also calculated for the relative increases and decreases in activation between each level of the task (i.e. 0- vs. 1-back, 0- vs. 2-back, 0- vs. 3-back, 1- vs. 2-back, 1- vs. 3-back, and 2- vs. 3-back). As with the previous analyses, these contrasts were calculated for both within and between groups.

Regions of significant activation were defined as those clusters of activation where the corrected probability level of the cluster was less than or equal to 0.05. In this study significant clusters were noted for all contrasts in the second level analysis.

While the original output from SPM99 gave the locations of voxels and clusters of significant activation in MNI co-ordinates, for the purposes of reporting these co-ordinates were

converted to a standard Talairach space (i.e. using non-linear transformation). The neuroanatomical descriptors of the anatomical locations of clusters of significantly altered activation were then determined using the Talairach Daemon database (Lancaster et al., 1997; Lancaster et al., 2000). This programme enables the user to input three-dimensional voxel co-ordinates (i.e. x, y, z) and based on this information generates an output file which describes the location of the voxels of interest with reference to the hemisphere, lobe, cortical description (i.e. cortical or subcortical) and Brodmann area (e.g. left hemisphere, frontal lobe, medial frontal gyrus, BA 8).

The outcomes of the analyses relating to the main factors of interest (i.e. the effect of participant group and the linear increase in difficulty of the n-back task) are outlined in the following sub-sections (full details of all clusters of significant activation relating to each of the experimental manipulations are available in Appendix 3A).

5.6.1 Control activation associated with performance of the n-back task: Block design

(Note: The extent of clusters of significant activation is noted for both the number of voxels comprised by the cluster (i.e. K_E) and the volume of the cluster (i.e. mm^3) based on an individual voxel volume of 8 mm^3 (i.e. 2 x 2 x 2 mm))

The pattern of activation seen in control participants during performance of the n-back task is depicted in Figures 5.10 – 5.12. In association with the parametric increase in difficulty of n-back, significant increases (i.e. $p_{(corrected)} \leq 0.05$) in activation were noted in control participants in the right inferior parietal lobule (BA40; cluster size (K_E)/vol. = 1428/11424 mm^3, $p < 0.001$), the left superior parietal lobule (BA40; K_E/vol. = 639/5112 mm^3, $p < 0.001$), the right medial frontal gyrus (BA8; K_E/vol. = 116/928 mm^3, $p = 0.004$) and the middle frontal gyrus, bilaterally (BA6, 9, 10 and 46; K_E/vol. = 244/1952 mm^3, $p < 0.001$; K_E/vol. = 458/3664 mm^3, $p < 0.001$; K_E/vol. = 407/3256 mm^3, $p = 0.001$; K_E/vol. = 144/1152 mm^3, $p = 0.028$; K_E = 79/632 mm^3, $p = 0.004$).

With the same changes in the experimental parameters significant decreases in activation were noted in a number of regions of cortex. In the left hemisphere significant clusters were observed in the cingulate gyrus (BA31; K_E/vol. = 2945/23560 mm^3, $p < 0.001$), the medial frontal gyrus (BA11/8; K_E/vol. = 4461/35688 mm^3, $p < 0.001$), the fusiform gyrus (BA37;

K_E/vol.=158/1264 mm^3, $p < 0.001$ and K_E/vol. = 104/832 mm^3, $p = 0.007$), the cuneus (BA19; K_E/vol. = 172/1376 mm^3, $p < 0.001$) and the insula (BA43/52; K_E/vol. = 224/1792 mm^3, $p < 0.001$). Regions of significantly decreased activation in the right hemisphere in controls included the precentral gyrus (BA13; K_E/vol. = 1211/9688 mm^3, $p < 0.001$), the parahippocampal gyrus (BA28/37; K_E/vol. = 157/1256 mm^3, $p < 0.001$), the middle frontal gyrus (BA11; K_E/vol. = 80/640 mm^3, $p = 0.026$), the middle occipital gyrus (BA18; K_E/vol. = 83/664 mm^3, $p = 0.022$), the lingual gyrus (BA18; K_E/vol. = 94/752 mm^3, $p = 0.012$), and the culmen (K_E/vol. = 242/1936 mm^3, $p < 0.001$). Moreover, decreased activation was seen bilaterally in the middle temporal (BA21 & 22; K_E/vol. = 145/1160 mm^3, $p = 0.001$ and K_E/vol. = 87/696 mm^3, $p = 0.018$) and superior temporal (BA22; K_E/vol. = 167/1336 mm^3, $p < 0.001$ and K_E/vol. = 94/752 mm^3, $p = 0.012$) gyri.

5.6.2 Patient activation associated with performance of the n-back task: Block design

The following images (i.e. Figure 5.13 – 5.15) illustrate the regions of significant increase and decrease in activation associated with the increase in task difficulty of the n-back task in the depressed patients. With an increase in a significant increase was observed in patients in the left hemisphere in the cerebellum (i.e. pyramis and declive; K_E/vol. = 229/1832 mm^3, $p < 0.001$), and a trend towards significance was noted in the left lingual gyrus (BA18; K_E/vol. = 60/480 mm^3, $p = 0.055$). In the right hemisphere significant increases were noted in the inferior frontal gyrus (BA46 & 47; K_E/vol. = 300/2400 mm^3, $p < 0.001$ & K_E/vol. = 165/1320 mm^3, $p < 0.001$), the inferior parietal lobule (BA40; K_E/vol. = 2817/22536 mm^3, $p < 0.001$), and the middle frontal gyrus (BA10; K_E = 412/3296 mm^3, $p < 0.001$ & K_E/vol. = 99/792 mm^3, $p = 0.004$). A significant bilateral increase was also seen in the superior frontal gyrus (BA6; K_E/vol. = 868/6944 mm^3, $p < 0.001$ & K_E = 576/4608, $p < 0.001$).

Significant decreases associated with increasing task difficulty were seen in the depressed patients in the left hemisphere in the medial frontal gyrus (BA10; K_E/vol. = 1071/8568 mm^3, $p < 0.001$), the superior temporal gyrus (BA22 & 41; K_E/vol. = 134/1072 mm^3, $p = 0.001$ & K_E/vol. = 145/1160 mm^3, $p < 0.001$), and the posterior cingulate (BA31; K_E/vol. = 1270/10160 mm^3, $p < 0.001$). Significant decreases were also observed in depressed patients in the following regions in the right hemisphere: transverse temporal gyrus (BA41; K_E/vol. = 617/4936 mm^3, $p < 0.001$); precentral gyrus (BA4; K_E/vol. = 104/832 mm^3, $p = 0.003$); cingulate gyrus (BA24; K_E/vol. = 157/1256 mm^3, $p < 0.001$); and the middle temporal gyrus (BA38; K_E/vol. = 108/864

mm^3, p = 0.002). A decrease in activation was also noted bilaterally in the cerebellum (i.e. uvula and pyramis; K_E/vol. = 83/664 mm^3, p = 0.012, and the culmen; K_E/vol. = 83/664 mm^3, p = 0.012 & K_E = 66/528 mm^3, p = 0.036) in patients.

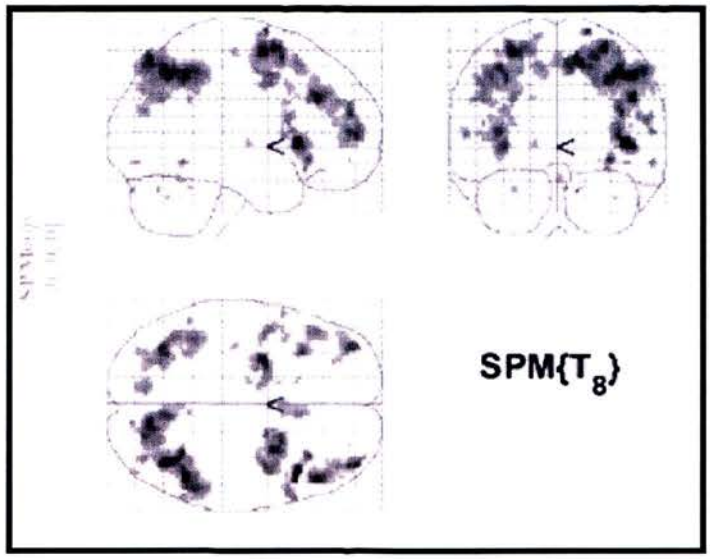

Figure 5.10: Statistical parametric map of the voxels of increased activation in the control participant group (i.e. N = 9) with the linear increase in difficulty of the n-back task – Experiment two: Random effects.

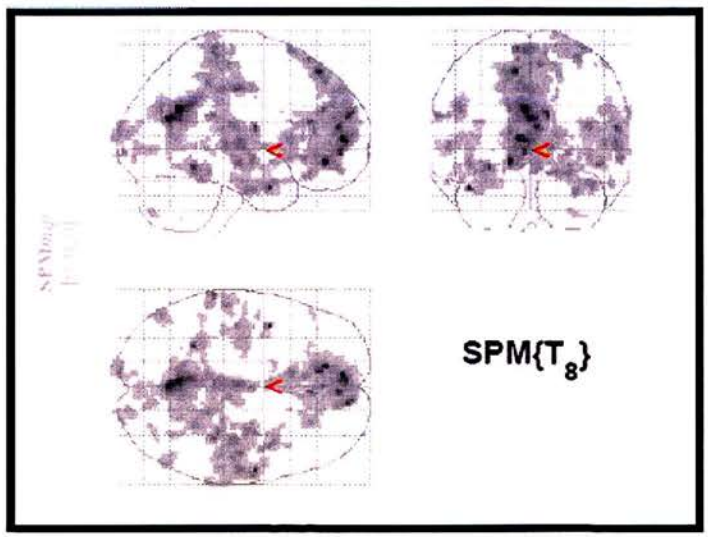

Figure 5.11: Statistical parametric map of the voxels of decreased activation in the control participant group (i.e. N = 9) with the linear increase in difficulty in the n-back task – Experiment two: Random effects.

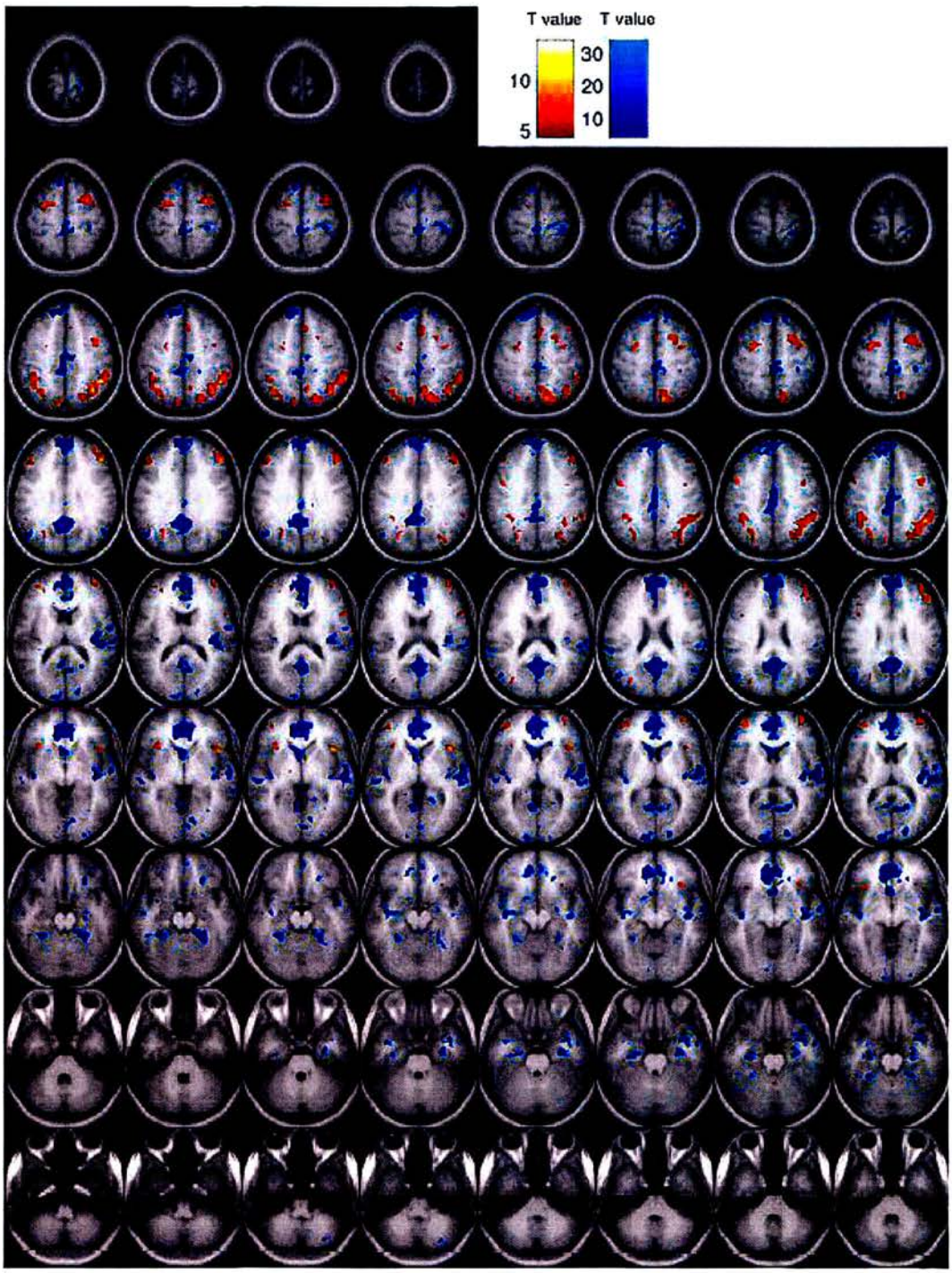

Figure 5.12: Increased (red colour scale) and decreased (blue colour scale) activation in controls with associated with the linear increase in difficulty of the n-back task – Experiment two (random effects, $p_{corrected} \leq 0.05$). The significant activations are superimposed 2D slices of a normalised, mean EPI image (i.e. image based on data obtained from 12 normal, healthy participants).

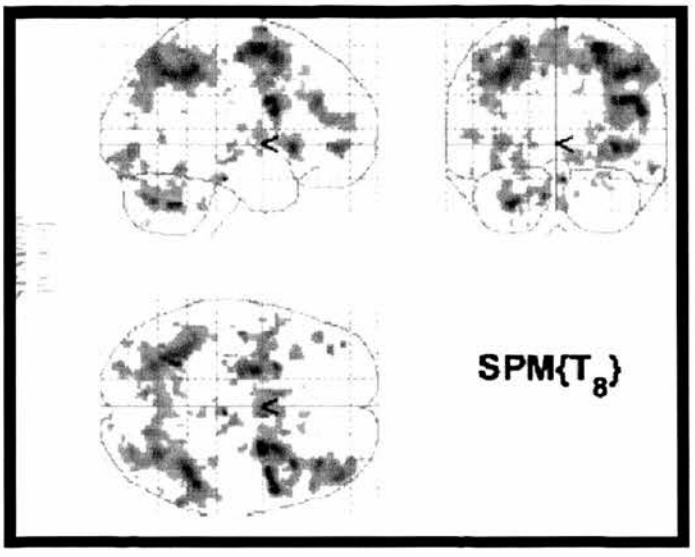

Figure 5.13: Statistical parametric map of the voxels of increased activation in depressed patients (i.e. N = 9) associated with the linear increase in task difficulty of the n-back task – Experiment two: Random effects.

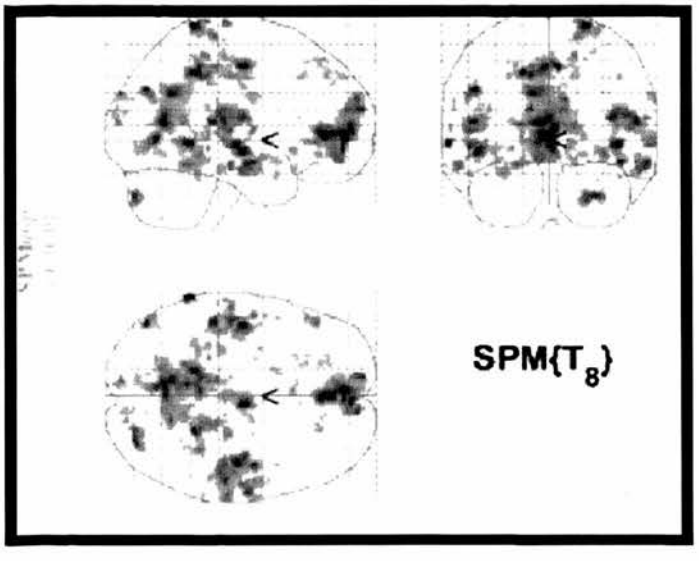

Figure 5.14: Statistical parametric map of the voxels of decreased activation in depressed patients (i.e. N = 9) associated with the linear increase in task difficulty of the n-back task – Experiment two: Random effects.

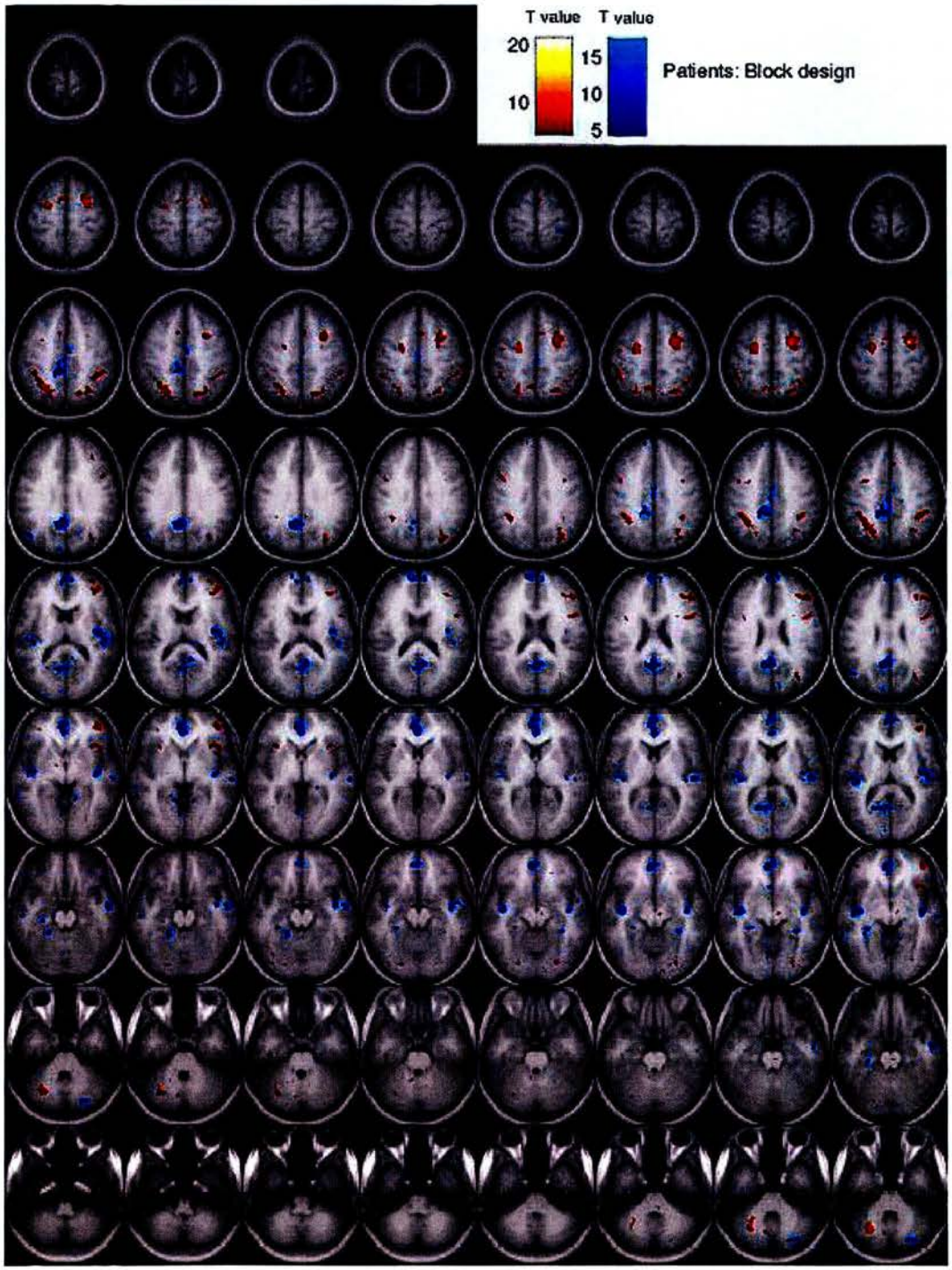

Figure 5.15: Increased (red colour scale) and decreased (blue colour scale) activation in patients associated with the linear increase in difficulty of the n-back task – Experiment two (random effects, $p_{corrected} \leq 0.05$). The areas of significant activation are superimposed on a normalised, mean EPI image (as before).

5.6.3 Comparison of areas of significant activation between patients and controls: Block design

Figure 5.16 & 5.17 depict the contrasts results of those cortical regions activation that differed in their degree of activation between patients and controls, associated with the increased difficulty of the n-back task. While there are a number of voxels that show group differences, significant differences were only evident in the medial orbital prefrontal cortex (MOPFC)/subgenual (rostral) anterior cingulate (rAC) (BA 12; K_E/vol. = 128/1024 mm^3, p = 0.025). This region was shown to be relatively more active in patients than controls with increasing difficulty of n-back

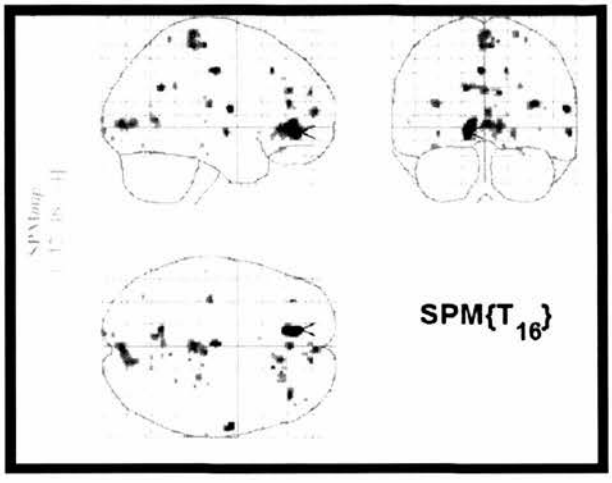

Figure 5.16: Statistical parametric map of the voxels of relatively increased activation in the depressed patients (i.e. N = 9) compared to the control participants (i.e. N = 9) associated with the linear increase in task difficulty of the n-back task – Experiment two: Random effects.

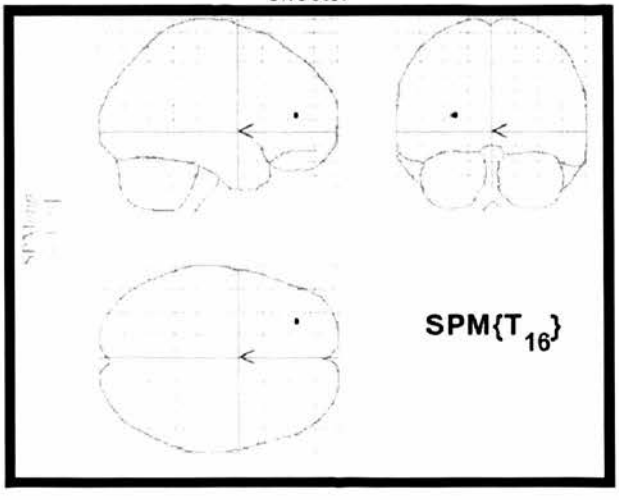

Figure 5.17: Statistical parametric map of the voxels of relatively decreased activation in the depressed patients (i.e. N = 9) compared to the controls participants (i.e. N = 9) associated with the linear increase in task difficulty of the n-back task – Experiment two: Random effects.

5.6.4 Correlation between regions of activation and severity of depression in MDD patients

In order to determine whether there was any significant contribution of the severity of depression to the pattern of activation seen in patients, a correlation analysis considering the relationship between signal intensity and HRSD score was conducted for depressed patients only. In order to achieve this the contrasts for increased and decreased activation with increasing difficulty of n-back were correlated with patients' HRSD score. The results of this random effects analysis can be seen in Figures 5.18 and 5.19. No statistically significant correlations were noted between clusters of significant increased or decreased activation and severity of depression. Indeed, even below threshold there were relatively few regions that displayed any association with the severity of depression in the patient group.

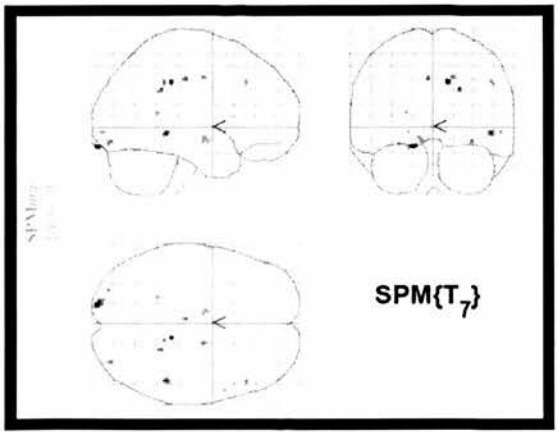

Figure 5.18: Statistical parametric map of the voxels of increased activation in the depressed patients (i.e. N = 9) that were correlated with the severity of depression as measured by the HRSD - Experiment two.

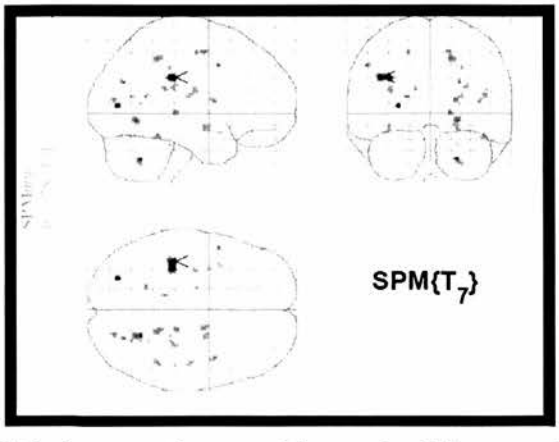

Figure 5.19: Statistical parametric map of the voxels of decreased activation in the depressed patients (i.e. N = 9) that were correlated with the severity of depression as measured by the HRSD – Experiment two.

5.7 Functional imaging results: Event related design

It was suggested that there might be a potential confounding effect of level of performance on the observed differences between patients and controls in the previous set of functional analyses. Therefore, it was deemed appropriate to consider the event-related activity associated with accurate task performance. More specifically, the areas of activation associated with correct responses only at each level of the n-back task were examined. As with the block-design analyses, the factors of interest in these analyses were the level of difficulty of the n-back task and the relative differences in activation between patients and controls.

The first step in this analysis was to plot all of the behavioural responses for each participant, across all levels of task difficulty. This was done in order to determine the general pattern of behavioural responses for both participant groups at each level of n-back. Of particular interest was whether, or not, there was a sufficient number of correct responses for each participant at each task level such as would justify their inclusion in the event related analysis. Once this had been assured, the behavioural data for each participant was then examined in order to determine the nature of each type of response, based on the following categories: i.e. correct actual response; correct no response; incorrect actual response; and incorrect no response. For the event related analysis the response type of interest was 'correct actual response'. Although it would have been interesting to examine the difference between correct and incorrect actual responses, both within and between participant groups, the number of incorrect actual responses at all levels of task difficulty was not sufficient enough to result in a large enough number of corresponding functional images, such as would have been required for meaningful analysis of the EPI data. Following identification of correct actual responses the timing of each correct response for each participant was identified, i.e. the time at which the stimulus item occurred relative to the beginning of the n-back paradigm. The timing of all correct actual responses for each participant was then saved to a text file, which was later used as an input file in the functional imaging analysis to identify the relevant images for each correct response for individual participants at each level of difficulty of n-back according to onset time.

After the determination of the fixed effects contrasts were calculated for individual participants in order to determine the voxels of significant activation associated with correct

items only at each level of n-back and those associated with the linear increase in task difficulty. As with the block design analysis for this study, our main interest was in voxels of significant activity that exhibited either a parametric increase or decrease in accordance with the parametric increase in the level of n-back. However, in this instance only those modulations of activation that were associated with correct actual responses were of interest, both within and between experimental groups.

In the calculation of the event related fixed effects analysis the haemodynamic response time was accounted for using the default Haemodynamic Response Function in SPM99. This particular function of SPM99 can be used to ensure that the haemodynamic response time is taken into account when determining the relevant functional images of interest. Failure to take note of this potential confounder may result in discrepancy between the actual event of interest and the measured 'event', thus impacting upon the reliability of the analysis of the functional imaging data.

An additional potential confounding effect in the event related analysis was the discrepancy between the TR (i.e. 2.5 seconds) and the ISI that was used in the n-back paradigm (i.e. 3 seconds). However, it is a feature of SPM99 that these two parameters need not match exactly. Indeed, SPM99 can take account of this potential discrepancy in the analysis of functional imaging data. This is achieved by computing the predictors of brain activity on a very fine resolution in time and than resampling them at a lower resolution to have one single value per volume.

As with the previous neuroimaging analysis, the first level, fixed effects contrasts for individual participants were utilised in the second level, random effects analysis. Random effects contrasts were calculated for within and between participant groups. Of interest were regions that exhibited an increase or decrease in activation associated with the increase in task difficulty, for correct actual responses only. In identifying clusters of significant change in activation the critical value of the corrected probability level was 0.05. Regions of significant cortical activation were determined by converting MNI co-ordinates to standard Talairach space. The Talairach co-ordinates were then used to identify the relevant cortical regions of interest, i.e. using the Talairach Daemon Database. Although various comparisons were made between the activation associated with correct responses at each of

the various levels of n-back, in the following sub-sections only those data relating to the overall linear increase in task difficulty are reported (Note: details of all significant findings can be viewed in Appendix 3B).

5.7.1 Control activation associated with performance of the n-back task: Event related

The pattern of activation associated with correct responses only in control participants is depicted in the following figures (i.e. Figure 5.18 – 5.20). Increased activation was noted in the left hemisphere in the inferior frontal gyrus (BA46; K_E/vol. = 164/1312 mm^3, $p < 0.001$) and in the following regions in the right hemisphere: inferior parietal lobule (BA40; K_E/vol. = 3346/26768 mm^3, $p < 0.001$ & K_E/vol. = 68/544 mm^3, $p = 0.028$); superior temporal gyrus (BA6; K_E/vol. = 73/584 mm^3, $p = 0.018$); and the thalamus (K_E/vol. = 132/1056 mm^3, $p < 0$ .001). Increased activation was also seen bilaterally in the middle frontal gyrus (BA10/8; 6; 10; & 9; K_E/vol. = 212/1696 mm^3, $p < 0.001$; K_E/vol. = 2011/16088, $p < 0.001$; K_E/vol. = 77/616 mm^3, $p = 0.014$; and K_E/vol. = 65/520 mm^3, $p = 0.033$), the insula (BA43/52; K_E/vol. = 339/2712 mm^3, $p < 0.001$ & K_E/vol. = 144/1152 mm^3, $p < 0.001$), and the cerebellum (i.e. declive, culmen, and tuber; K_E/vol. = 250/2000 mm^3, $p < 0.001$; K_E/vol. = 268/2144 mm^3, $p < 0.001$;.and K_E/vol. = 103/824 mm^3, $p = 0.002$).

Decreased activation associated with correct responses only was noted in controls as the level of difficulty of n-back increased in a number of clusters. In the left hemisphere regions of significantly decreased activation associated with accurate performance of the task included both posterior and anterior cingulate cortex (BA23 & 24/25; K_E/vol. = 1624/12992 mm^3, $p < 0.001$ & K_E/vol. = 149/1192 mm^3, $p < 0.001$) and in the angular gyrus (BA39; K_E/vol. = 181/1448 mm^3, $p < 0.001$). Bilaterally decreased activation was noted in the following areas: insula (BA43/52; K_E/vol. = 1032/8256 mm^3, $p < 0.001$ & K_E/vol. = 63/504, $p = 0.039$; medial and superior frontal gyri (BA9/6; K_E/vol. = 2695/21560 mm^3, $p < 0.001$); parahippocampal and fusiform gyri (BA20 & 37; K_E/vol. = 221/1768 mm^3, $p < 0.001$; K_E/vol. = 122/976 mm^3; $p < 0.001$; & K_E/vol. = 108/864 mm^3; $p = 0.002$); paracentral lobule (BA5; K_E/vol. = 380/3040 mm^3, $p < 0.001$); middle temporal gyrus (BA21; K_E/vol. = 202/1616 mm^3, $p < 0.001$; K_E/vol. = 86/688 mm^3, $p = 0.007$; & K_E/vol. = 161/1288 mm^3, $p < 0.001$); and superior temporal gyrus (BA40 & 41; K_E/vol. = 132/1056 mm^3, $p < 0.001$ & K_E/vol. = 59/472 mm^3, $p = 0.052$).

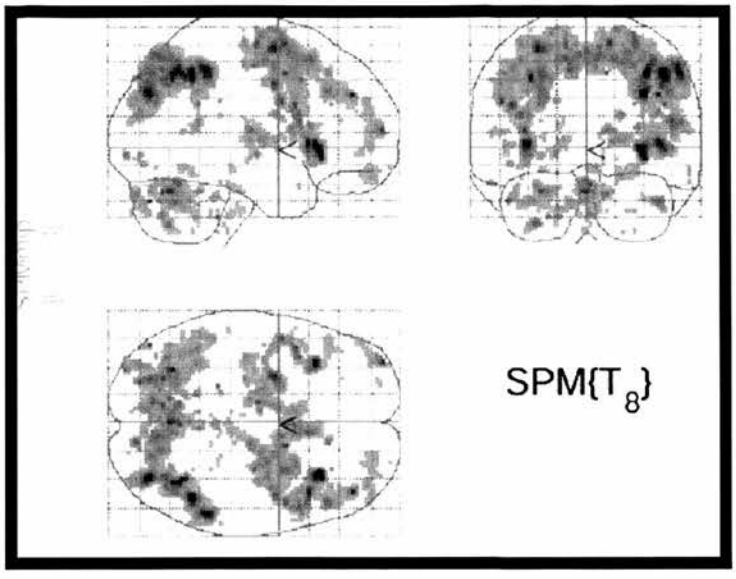

Figure 5.20: Statistical parametric map of the voxels of significantly increased activation in the control participants (i.e. N = 9) associated with the linear increase in difficulty of the n-back task – Experiment two: Correct responses only (random effects).

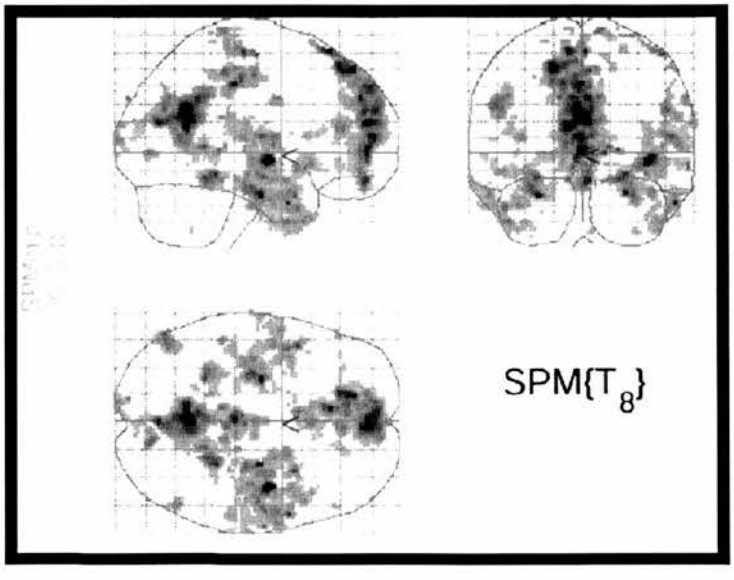

Figure 5.21: Statistical parametric map of the voxels of significantly decreased activation in the control participants (i.e. N = 9) associated with the linear increase in difficulty of the n-back task – Experiment two: Correct responses only (random effects).

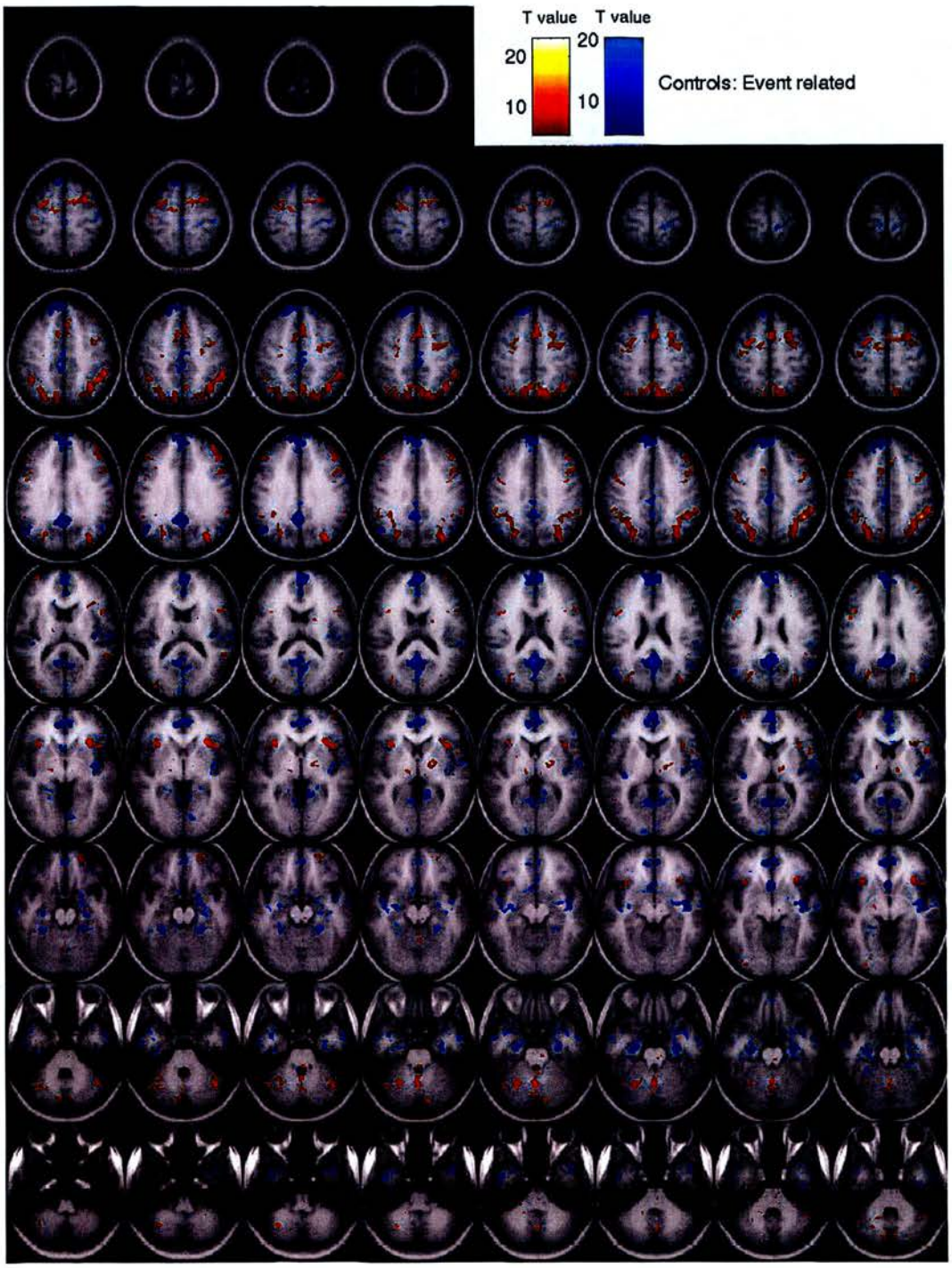

Figure 5.22: Increased (red colour scale) and decreased (blue colour scale) activation in controls with increasing task difficulty – Experiment two: Correct responses only (random effects). (Random effects, $p_{corrected} \leq 0.05$). Mean increase and decrease areas of activation are superimposed upon normalised, mean EPI image (as before).

5.7.2 Patient activation associated with performance of the n-back task: Event related

The pattern of activation observed in patients during accurate performance of the task was similar to that seen in controls (see Figures 5.21 – 5.23). Increased activation was seen in the left hemisphere in a cluster covering the precuneus and postcentral gyrus (BA7; K_E/vol. = 192/1536 mm^3, $p < 0.001$) and in the cerebellum (i.e. declive and tuber; K_E/vol. = 228/1824 mm^3, $p < 0.001$). In the right hemisphere significant increases in activation associated with correct responses with increasing difficulty were seen in the insula (BA43/52; K_E/vol. = 124/992 mm^3, $p < 0.001$), the precentral and middle frontal gyri (BA9 & 6; K_E/vol. = 366/2928 mm^3, $p < 0.001$ & K_E/vol. = 255/2040 mm^3, $p < 0.001$), in the medial frontal gyrus (BA6/8; K_E/vol. = 293/2344 mm^3, $p < 0.001$), and in a region comprising the precuneus and the middle temporal gyrus (i.e. BA 19; K_E/vol. = 436/3488 mm^3, $p < 0.001$). In addition, increased activation was seen bilaterally in the inferior parietal lobule (BA40; K_E/vol. =861/6888 mm^3, $p < 0.001$ and K_E = 239/1912 mm^3, $p < 0.001$).

As with the increased activation, the pattern of decreased activation seen in patients during correct responses was similar to that seen in controls. In the left hemisphere a significant accuracy associated decrease was noted in the superior frontal gyrus (BA8; K_E/vol. = 451/3608 mm^3, $p < 0.001$) and in clusters involving the precuneus, the medial frontal gyrus and the paracentral lobule (BA7/6/5; K_E/vol. = 2514/20122 mm^3, $p < 0.001$), and the inferior frontal and subcallosal gyri (i.e. BA25/44; K_E/vol. = 63/504 mm^3, $p = 0.036$). Significant decreases in the right hemisphere were seen in the precentral gyrus (BA6; K_E/vol. = 70/560 mm^3, $p = 0.021$), in the cuneus and precuneus (BA19; K_E/vol. = 159/1272 mm^3, $p < 0.001$), in the medial frontal gyrus (BA10; K_E/vol. = 1336/10688 mm^3, $p < 0.001$), and in a cluster comprising the insula and the precentral gyrus (BA43/52; K_E/vol. = 322/2576 mm^3, $p < 0.001$). Moreover, significant decreases were observed bilaterally in a number of clusters involving the middle temporal gyrus (BA39 & 21; K_E/vol. = 99/792 mm^3, $p = 0.033$; K_E/vol. = 196/1568 mm^3, $p < 0.001$; K_E/vol. = 145/1160 mm^3, $p < 0.001$; & K_E/vol. = 59/472 mm^3, $p = 0.049$), the lingual gyrus (BA19; K_E/vol. = 83/664 mm^3, $p = 0.008$ & K_E/vol. = 66/528 mm^3, $p = 0.029$), and the cerebellum (i.e. uvula and culmen; K_E/vol. = 74/592 mm^3, $p = 0.016$ & K_E/vol. = 201/1608 mm^3, $p < 0.001$).

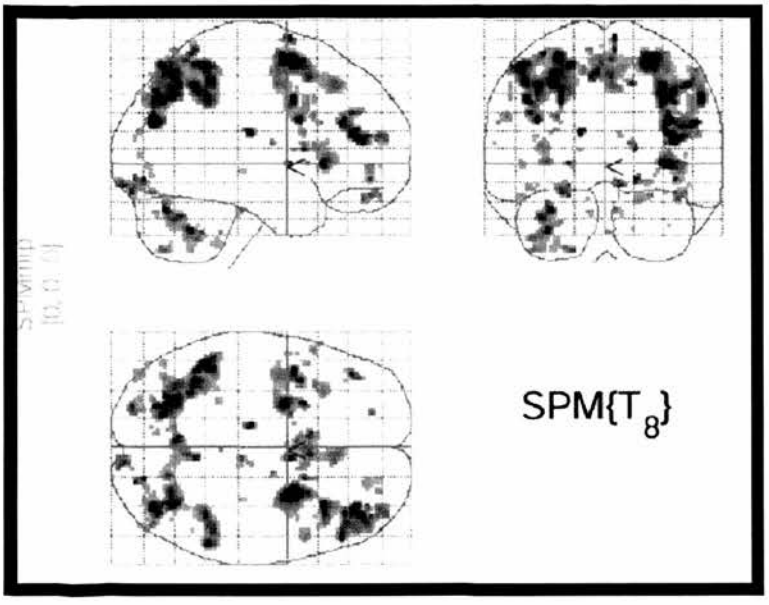

Figure 5.23: Statistical parametric map of voxels of increased activation in depressed patients (i.e. N = 9) associated with the linear increase in difficulty of the n-back task – Experiment two: Correct responses only (random effects).

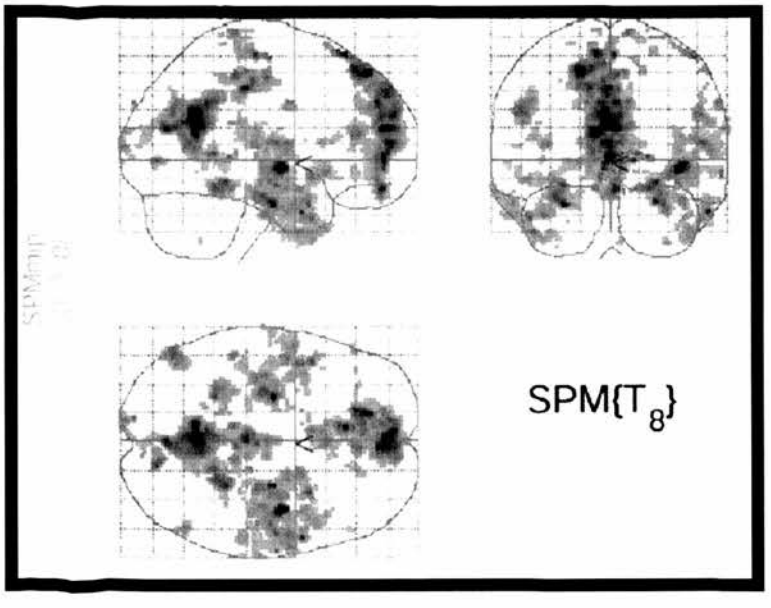

Figure 5.24: Statistical parametric map of the voxels of decreased activation in depressed patients (i.e. N = 9) associated with the linear increase in difficulty of the n-back task – Experiment two: Correct responses only (random effects).

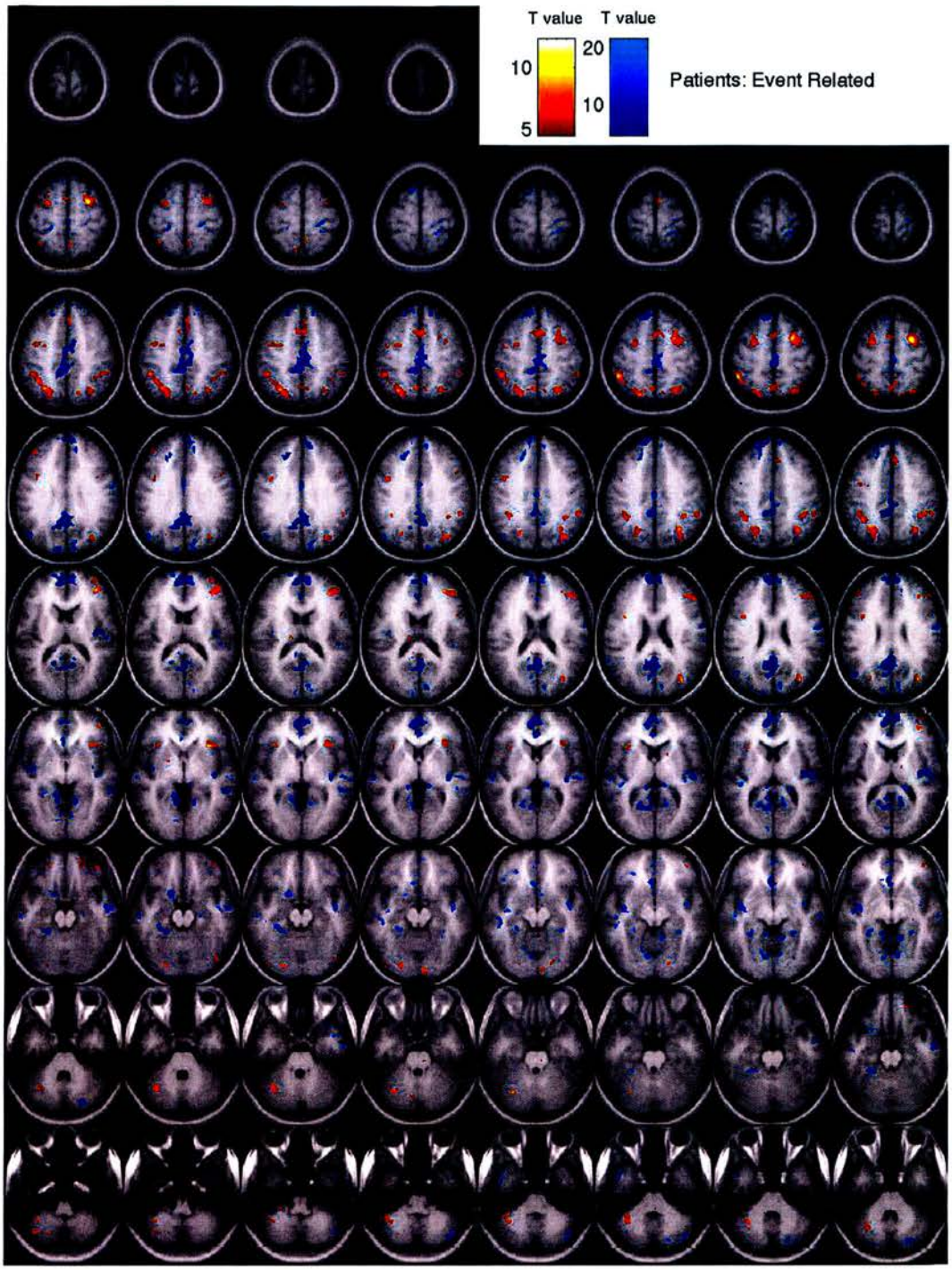

Figure 5.25: Increased (red colour scale) and decreased (blue colour scale) in patients with increasing task difficulty – Experiment two: Correct responses only (random effects; $p_{corrected} \leq 0.05$). Mean increased and decreased activations are superimposed on normalised, mean EPI image (as before).

5.7.3 Comparison of areas of significant activation between patients and controls during performance of the n-back task: Correct responses only

The contrasts that were calculated to compare the cortical activation of patients and controls on correct responses only revealed no significant differences between groups (see Figure 5.24). As with the other contrasts, this comparison was concerned with those activations associated with the linear increase in task difficulty. However, additional comparisons of the relative activations of the two groups at the various levels of the task also revealed no statistically significant differences between the groups when comparing correct responses only.

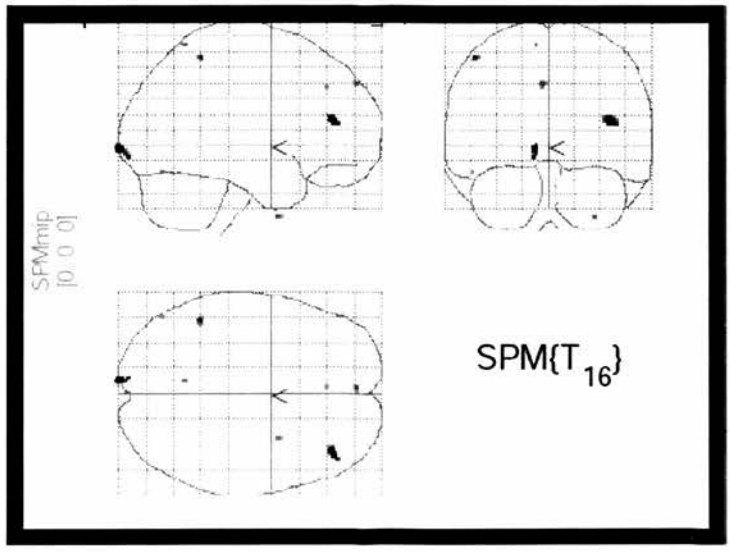

Figure 5.26: Statistical parametric map of the areas of relative increase in depressed patients (i.e. N = 9) compared to control participants (i.e. N = 9) associated with the linear increase in difficulty of the n-back task – Experiment two: Correct responses only (random effects).

Chapter 6: Methodology - Experiment Three

6.1 Design

Experiment three used a counter-balanced cohort design to test the experimental hypotheses (see Chapter 1: pp 90). As with the previous studies that made up this project, the primary within-subjects factor in this investigation was the level of difficulty of the n-back task (i.e. 0-, 1-, 2-, and 3-back). However, in the case of the current experiment, there was also the additional within-subjects factor of medication status (i.e. medication-free vs. post-medication).

With respect to behavioural performance, the dependent variables of interest were accuracy (i.e. percentage of correct responses) and reaction time (in milliseconds) at each level difficulty of the n-back. The analyses of the behavioural results of participants were designed to determine the main effect of level of difficulty of n-back and medication status on measures of performance of the n-back task. Moreover, these analyses also took account of the potential interaction between level of difficulty and medication status on participant performance.

As in second study in this series, performance on the n-back task was assessed while participants underwent BOLD EPI functional neuroimaging. However, in this study participants underwent two complete scanning trials, i.e. one scan while medication-free and a second scan following the subacute administration of anti-depressant medication. During each of these scanning trial participants underwent two separate scanning sessions (i.e. session 1 vs. session 2). The functional imaging data acquired during both of these scanning sessions were analysed in order to ascertain the level of cerebral activation associated with the increasing difficulty of the n-back task, and for relative increases and decreases in activation associated with the change in medication status. The comparison of functional activation between conditions was based on the differences in pattern of increased and decreased activation associated with the linear increase in difficulty of n-back in participants while medication-free and post-medication. The contrasts relevant for each comparison were calculated for both first and second scanning session independently, and for the overall pattern of activation across both imaging sessions.

6.2 Participants

6.2.1 Participant recruitment

The recruitment and testing of participants in this study were covered by the ethical approval of the Lothian NHS board, Psychiatry and Psychology Research Ethics Committee, and by management approval from the board of the Lothian Primary Care NHS Trust.

In a method similar to the previous studies, participants for experiment three were opportunistically sampled, using a combination of prospective sampling and word of mouth. Individuals were approached who fulfilled the criteria for inclusion and had expressed an interest in participation. The criteria for inclusion were the same as the criteria used to screen control participants in experiment two (see Chapter 4). In addition, it was also ensured that participants would not be taking any other medication at the proposed time of participation, which might have interacted negatively with the medication they were required to take in the current experiment. These criteria resulted in an experimental sample of participants that were free of any physical or psychological condition such as would have a potential effect on both the behavioural and functional neuroimaging data, and thus exclude them from participation in this type of study.

Individuals who volunteered to participate in the study were given an information pack, which detailed the requirements for participation and the nature of the study (see section 6.3.1). Participants were given a minimum of 48 hours to read this information and to decide whether they were both suitable for participation and would be willing to take part. In a similar approach to experiments one and two, it was verbally reiterated to volunteers that participation was on an entirely voluntary basis, that if they should decide to participate they were free to withdraw at any time and without giving a reason, and that they should feel free to discuss participation with any relevant parties, including friends, relative, and the experimental investigators. While the sample of individuals approached to take part did include persons known to the researchers no participant was involved in a dependent relationship with either of the investigators.

Prior to giving consent to participate, volunteers were informed that for taking part in the study they would receive a cash payment of £50.00. As a result of the number and length of testing sessions participants were required to complete for this investigation, this payment

was given as a means to cover expenses incurred as a result of participation. Participants were further advised that they would receive a proportion of the expenses payment for each phase of the study that they completed, i.e. £10.00 for the pre-test session and £20.00 for each functional imaging session. It was thought that be allocating the payment in this manner, rather than giving a single payment for completing all stages, would prevent participants from feeling under an obligation to complete the study in order to obtain the payment

Given that this experiment involved giving anti-depressant medication to a non-clinical population, a stipulation of ethical approval was the provision of information regarding participation to each participant's general practitioner. The reasons for this were twofold. Primarily, this measure was included so as to alert GPs to the participation of their patients, in order that they could notify the investigators of any medical reason for individuals not to take part in the study. The second reason for this approach was the desire to ensure that details of participation were appended to an individual's medical records. Therefore, if during the course of the study or in the future there was any medical relevant outcome relating to the consumption of the medication used in the investigation then the participant's doctor would have prior knowledge of the situation.

Once all the necessary information had been obtained from each individual participant a letter was sent to his or her GP (see Appendix 2). A copy of both the participant information sheet and the consent form were attached to this letter. The letter informed the GP that their patient had consented to take part in the study and briefly outlined what would be expected of the participant. While GP's were not asked to provide the researchers with any clinical information about the participant they were requested to let the experimenters know if they had any concerns about their patient participating in the study.

6.2.2 Participant details

From those individuals who volunteered for participation, a sample of ten healthy, right-handed participants were chosen for participation, based on their ability to meet the relevant criteria for inclusion (i.e. 3 male and 7 female participants). Prior to participation these individuals were allocated to one of two experimental cohorts, i.e. Group A or Group B. The demographics of the two subgroups are outlined in Table 6.1.

Group (N)	*Ratio of male/female participants*	*Age (years): Mean (s.d)*	*IQ: Mean (s.d)*	*Years of education: Mean (s.d)*
Group A (5)	1/4	25.6 (2.7)	106.2 (8.0)	15.2 (1.9)
Group B (5)	2/3	23.6 (4.3)	105.8 (8.7)	15.0 (2.7)
Total (10)	3/7	24.6 (3.6)	106.0 (7.9)	15.1 (2.2)

Table 6.1: Demographic details of participants - Experiment three.

6.3 Materials (see Appendix 2)

6.3.1 Recruitment materials

The information pack given to individuals who expressed an interest in participation contained a copy of each of the following forms:

(a) Exclusion Criteria List

In order to ensure that participants were aware of the criteria for participation they were given a list of all experimental exclusion criteria (as previously outlined). This list detailed the physical and psychological criteria that participants were required to meet in order to be suitable for participation in experiment three.

(b) Information Sheet for Participants

The information sheet prepared for this experiment detailed the aims of the study, the methods of investigation, and the requirements of participation. The information sheet also explained what would be expected of individuals who did participate in the project and the possible effects that participation may have on them

(c) Medication Information Sheet

Although the information sheet for participants did highlight the potential side effects of taking the anti-depressant medication, participants were also provided with a separate information sheet containing information relating specifically to the recognized side effects of escitalopram.

The medication information sheet gave details about the medication that would be used in the study, i.e. escitalopram, and listed the most commonly experienced side effects associated with its prescription. The information regarding the previously documented side effects was adapted from information obtained from the website of company involved in the

manufacture of escitalopram oxalate in the United States (i.e. www.lexapro.com; accessed 25/10/2002). The information given here not only detailed potential side effects, the comparative incidence of these side effects in individuals taking escitalopram and those taking placebo medications were also noted.

(d) Statement on Compensation Arrangement

In order to ensure that participants were completely aware of the compensation policy associated with the sort of investigation, a separate form was included which outlined the conditions of compensation for participants involved in research at the University of Edinburgh. This form was included as part of the requirements of the relevant ethics committees.

(e) Consent Form

Each information pack also included two copies of the consent form for this study, i.e. one for the participant to keep and one to be returned to the investigators. This consent form asked participants to confirm that they had read the information provided and that they were willing to participate in the project based on this information. It confirmed to individuals that participation in the study was voluntary, and that they were free to withdraw at any stage, without giving a reason, and without their legal or medical rights being affected. In addition, the consent form also asked participants to acquiesce to the provision of details of their participation to their GP prior to taking part, and to acknowledge that if necessary their GP would be alerted to the acquisition of clinically salient information during the course of the investigation.

A practical requirement of the recruitment procedure was the acquisition of personal information from participants. Therefore, a copy of each of the following forms was also included in the information pack. Participants were asked to complete each form and return it, with their consent form, to the investigators.

(f) GP Information Sheet

On this form, participants had to complete name and contact details for their current GP.

(g) Personal Details Form

This form asked individuals to give their name and current contact details.

Each individual was also asked to provide details of their availability, outlining the dates and times which they were available for testing. In conjunction with the details of time and availability limitations of scanning sessions, the availability information for each participant was used to allocate participants to experimental cohorts.

The final pre-test measure was a medical history questionnaire (see Appendix 2). Given that it was essential for participants to meet the same inclusion criteria as control participants in the second investigation of this series, the same version of the medical history questionnaire that was developed for experiment two was also used in this study.

6.3.2 Behavioural measures

The following sections of this chapter detail those affective and cognitive measures that were employed in experiment three. More in-depth details of the nature and administration of measures that were used in this study, which were also employed in experiments one and two, can be viewed in Chapter 2.

6.3.2.1 Affective assessments

In order to ensure that the results of all of the investigations, which comprised this project, were consistent and comparable in their data acquisition, the same affective assessments that were employed in the previous studies were also used in this study.

Thus, the presence/absence of significant current depressive symptomology in participants at the time as test was assessed using the Beck Depression Inventory (Beck et al., 1961) was used. While, the Stress Arousal Checklist (Mackay et al., 1978) was used to measure state stress and arousal, and the Alderley Park State Anxiety Questionnaire (Walker, 1990) was employed as a measure of state anxiety.

6.3.2.2 Cognitive assessments

National Adult Reading Test (Nelson & Willison, 1991)

The NART was employed in order to estimate full scale WAIS-R IQ in eight of the participants in the group. However, the remaining two participants both identified themselves as being dyslexic. Despite the fact that both participants asserted that the level of impairment they experienced was relatively small, it was assumed that the NART might not provide the most accurate measure of IQ for these individuals. Given that participants were

already being asked to commit to relatively long testing session it was decided that conducting a full WAIS-R testing session would be out of the question. Therefore, a previously used short-form of this IQ test was used instead. The details of this form are as follows:

Four-Test Short Form WAIS-R

The short-form of the WAIS-R used in this investigation was developed by Reynolds, Willson & Clark, (1983) as an alternative to the full WAIS-R testing session. Although there are many different types of short-form WAIS-R assessments that have been conducted, each using a different selection of subtests, this particular variation provides an estimate of full scale IQ based on performance on four of the WAIS-R subtests, i.e. 'Information', 'Picture Completion', Arithmetic', and 'Block Design'.

This form of abbreviated WAIS-R was chosen for this investigation as it has previously been shown to have a reasonable level of validity. For example, IQ estimates based on Reynolds et al.'s (1983) short form of the WAIS-R were shown to not differ significantly from the actual full scale IQ in a population of adults with mild to severe traumatic brain injury (Guilmette et al., 1999). Thus, it was assumed that this form would not only allow for a significant reduction in testing time, but would also enable an accurate estimate of full scale IQ in those participants who had been identified as dyslexic.

Test of Everyday Attention (Robertson et al., 1994)

The same subtests of the TEA that were used in the previous two experiments were also used in experiment three, i.e. visual elevator and elevator counting with distraction. These tests were included as measures of selective attention, cognitive flexibility and auditory verbal working memory.

n-back task

The same version of the n-back paradigm that was developed for the scanning sessions in experiment two was also used in the experimental sessions of the current study. However, a new practice version of the task was created, which was designed to take account of the increased time involved in completion of the stages of this experiment, compared to the testing sessions of experiments one and two.

Although we already had the version of the task that was used in experiment one it was felt that this particular form was rather lengthy for the purposes of this study. There were two reasons for this. Primarily, participants were already being asked to give up a significant amount of their personal time and we were keen not to unnecessarily increase this amount of time. Secondly, given that participants would have to complete the task inside the scanner on two separate occasions it was decided it would be best to minimise exposure to the task in order to prevent both significant practice effects and potential boredom with the task. Therefore, a practice version of the n-back task was designed with the specific purpose of reducing the time taken to complete participant pre-testing.

Essentially, this was achieved by halving the number of trials of each level of n-back seen in the original version of the task, i.e. subjects were presented with five blocks each of 1-, 2-, and 3-back conditions interspersed with blocks of 0-back. As with the version of the task used in the pilot study each block of n-back only began when participants pressed the 'space' bar. Therefore, the practice run of the task was self-paced, with a minimum run time of approximately 15 minutes.

Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Majdan, Sziklas & JonesGotman, 1996)

In addition to the other cognitive assessments, a novel measure of cognitive function was included in this study, i.e. the RAVLT (Full details of the administration, scoring, and norms of the RAVLT can be found in Spreen, 1998). The RAVLT was employed in this study in order to assess the potential impact of the administration of escitalopram on factors pertaining to memory and learning. Indeed, this particular measure of has been designed to assess immediate memory span, novel learning, susceptibility to interference, and recognition memory (Spreen, 1998).

The variation of the RAVLT that was used was developed by Madjan and colleagues (i.e. Majdan et al., 1996), and consisted of two lists of 15 nouns each (i.e. List A and List B). The researcher read aloud the nouns on the first list (i.e. List A), pacing the speed at which they read in order to ensure a 1 second interval between each noun. After the last noun had been read participants were given a free-recall test, i.e. they were asked to recall as many items as they can from the list. The same procedure was then repeated until participants have

completed five consecutive trials. Once the fifth trial has been completed participants are read an 'interference' list (i.e. List B), and were asked to recall as many items as they could from this list. Immediately following the free-recall of List B participants were given a free-recall test of the items on List A. After an interval of 20 minutes participants were presented with a list of 50 nouns, containing all items from Lists A and B, and a number of distractor items. Participants were then asked to highlight those items that they recognised from List A only.

There are a variety of measures that can be obtained from the RAVLT, e.g. raw score, number of errors, type of errors etc. However, in this instance participants were allocated a score based on the total number of items correctly recalled/recognised at each stage of the assessment. While the number and types of errors that participants make are also noted they were not used in any of the data analyses in this study.

In order to ensure that there was no confounding effect of practice or long-term memory on participant's results in their second testing session, two different forms of this measure were used in the current investigation (i.e. Form 1 and Form 2; see Appendix 2).

Anti-depressant medication

There were two criteria for the choice of antidepressant medication that was used in experiment three. Primarily, it was felt that the type of medication used should be an accurate reflection of the types of medication that were being taken by patients in experiment two, in order to make the findings of the two studies more comparable. Secondly, ethical considerations dictated that the choice of medication should be one that would be less likely to induce negative side effects. Therefore, the medication that was chosen for experiment three was a selective serotonin reuptake inhibitor, escitalopram (also known as 'Cipralex' (UK) or 'Lexapro' (USA)). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram (see Figure 6.1). Escitalopram is a more modern medication than its parent compound, and as such can be administered in lower effective doses and has reduced side effects. These qualities have been attributed to the lack of the inactive R-isomer that comprised citalopram.

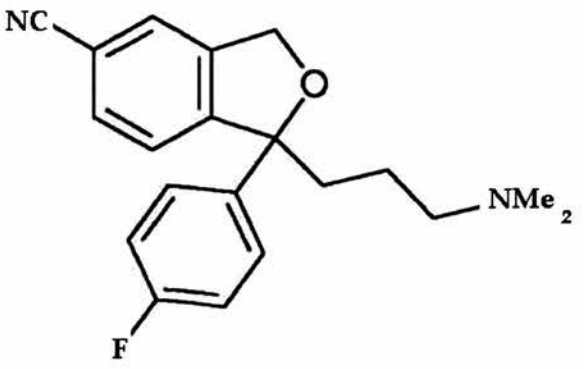

Figure 6.1: Chemical structure of escitalopram

Escitalopram is normally administered a film coated, round tablets containing escitalopram oxalate in strengths equivalent to 10 mg and 20 mg escitalopram base. Participants in this study were prescribed 10mg tablets. Although this dose is greater than the minimal effective dosage of 5 mg, it was felt that as a subacute administration method used in this study, this slightly higher dose would be more representative of the dose levels seen in patients. The tablets given to participants also contained the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate.

Scanner specifications

All participants were scanned in a 1.5 T GE Signa MRI scanner, which was located at the SHEFC Brain Imaging Research Centre, at the Western General Hospital, Edinburgh.

BOLD sensitive echo planar fMRI images were acquired with a TR of 2.5 seconds, and a TE of 40 milliseconds. The flip angle was 90^0, with a field of view of 24 cm. In addition, the in plane resolution was 64 x 64, with a plane orientation that was near axial. All functional scans were 5mm in thickness with no slice gap, thus a total of 30 slices were obtained. Data was acquired over two functional sessions, with each functional acquisition being 18 minutes 55 seconds in length.

T2 and T1 weighted structural images were also obtained for each participant. The scanning parameters used for these structural acquisitions were identical to those employed in the previous study (see Chapter 4, Table 4.3 for full details).

6.4 Procedure

6.4.1 Pre-test procedure

As noted, individuals who expressed an interest in participation were given an information pack a minimum of 48 hours prior to participation. If participants were able to confirm that they met all of the criteria for inclusion in the study and had read both of the information sheets, they were asked to complete the three consent forms, the GP information sheet, the availability form, and the personal details form. They were advised to retain one copy of the consent form and the information sheets for their own records and to return all other completed forms to the researchers.

Following completion of each of these pre-test measures participants were allocated to one of the two experimental groups (i.e. five each to Group A and Group B). Although it would have been ideal to randomly allocate participants to their sub-groups the relatively small number of participants and the difficulties associated with scheduling, for both parties, meant that participants were largely allocated to groups based upon the personal availability and the availability of the scanner for testing.

Given the potentially sensitive nature of the data that was collected from participants, prior to commencing the affective and neuropsychological assessments individuals were reassured that all information about them that was acquired during the course of the study was entirely confidential and that all data would be coded in such a way as to make their individual contributions to the data set undecipherable to any persons other than the key investigators.

6.4.2 Procedure: Group A

6.4.2.1 Phase 1: Pre-scanning assessment

Initially individuals in Group A were invited along for a preliminary assessment phase. For participants in this group this initial assessment occurred on the same day as the first scanning session, prior to commencement of scanning (i.e. Day 1). The assessments that participants completed during this session were as follows:

Pre-test measures

They were asked to complete the medical history and pre-scan questionnaires, in order to confirm their suitability for participation.

Affective assessments

Following completion of the pre-test measures, participants undertook the necessary affective assessments, i.e. the BDI, the SAC, and the APSAQ. Although all participants were asked to confirm that they had no history of psychiatric illness the BDI was used to indicate whether, or not, there was any significant current level of depressive symptomology. Based on the standard rating procedures, a score of 9 or more on this assessment at this stage was deemed to be indicative of a mild level of depression, and therefore a reason to automatically exclude an individual from participation. The other affective measures were simply used to give an indication of state stress, arousal, and anxiety.

These measures were completed at this initial stage in order to provide a baseline measure of current affective state, which could then be compared to the affective state of participants in the post-medication condition.

Cognitive assessments

Each individuals WAIS-R full scale IQ was estimated using one of the two methods outlined above. Completion of the IQ assessment was followed by the two TEA subtests, and the initial stages of the RAVLT.

The practice version of the n-back task then served as a distracter task between the initial recall and later recognition phases of the RAVLT. After a period of at least 20 minutes participants were then asked to complete the RAVLT.

Prescription of medication

Following completion of the various cognitive measures participants met with a medical practitioner in order to obtain their course of medication. Participants were provided with 7, 10 mg escitalopram oxalate tablets. They were advised to consume one tablet per day for the next seven days, i.e. commencing the course of medication on the day following the initial assessment and primary scan phases.

It confirmed with participants that they understood the nature of the medication they would be taking and that they knew of no reason why they should not take the medication. Furthermore, they were provided with 24-hour contact details, which they were advised

they should use to contact the researchers if at any point during the study they felt unwell or had any concerns.

6.4.2.2 Phase 2: Medication free scan

As already noted above, the first scanning session for individuals in Group A occurred on the same day as the pre-scanning assessment. Therefore, all the necessary pre-scanning affective and cognitive assessments had already been completed prior to scanning.

The scanning protocol in this experiment was identical to the protocol in experiment two (see Chapter 4 for details). In brief, participants completed two BOLD EPI functional MRI sessions, each lasting 18 minutes 55 seconds. During each session they completed a number of blocks of each of the various levels of the n-back task. In addition to the attainment of the functional imaging data, T1 and T2 weighted structural images were also acquired for each participant.

6.4.2.3 Phase 3: Post-medication scan

On the day that participants took the final dose of escitalopram (i.e. Day 8), and not longer than 6 hours after they had taken the last tablet, they attended for their second scanning session.

Prior to scanning participants again completed each of the affective and cognitive assessments that they had undertook in their first experimental phase (with the exception of the NART/WAIS-R). Participants first of all completed the initial free recall (both repeated and interference tests) phase of the RAVLT, i.e. using the second, previously unseen version of the task. In order to provide individuals with some sort of distracter task, this initial phase was followed by each of the affective assessments and the two TEA subtests. After an interval of at least 20 minutes, and completion of the other measures participants were presented with the recognition phase of the RAVLT.

Additional information obtained from participants at this point included details of the time at which they had taken the final dose of escitalopram, any side effects they had experienced while taking the medication, including the frequency and duration of these side effects, and how severe they felt these side effects to be.

Blood sampling

On the day of the second scan, and prior to scanning, participants provided a blood sample (10mL), which was collected by venipuncture (ante-cubital vein) into lithium heparin. The date and time of sampling were recorded. Plasma was separated by centrifugation and the plasma was stored in clearly labelled tubes at –20°C. Plasma was later analysed for total S-citalopram and total N-desmethylcitalopram (norcitalopram) using high-performance liquid chromatography. This procedure was carried out by Dr Edgar Spencer and his team at Guy's and St. Thomas' Hospital, London, UK.

After they had provided the necessary blood sample, participants underwent the second scanning session. The protocol for this session was exactly the same as for the first session, with the exception that there was no practice phase inside the scanner.

6.4.3 Procedure: Group B

While the procedure of each of the individual phases, i.e. initial assessment phase, medication-free phase, and post-medication phase, was identical for participants in Group B, the phase order was altered.

On day 1, participants attended for the initial assessment phase, after which they were given their prescription of escitalopram, i.e. 10mg/day for 7 consecutive days. On day 8 (i.e. the final day on which they took the medication) they attended for their 'post-medication' scan. A further 7 days later (i.e. day 15) they attended for their 'medication-free' scan.

6.4.4 Data analysis

Full details of the analyses conducted on both the behavioural and functional data can be seen in Chapter 7. However, in brief, the main analyses were as follows:

6.4.4.1 Behavioural Data

The behavioural data were analysed using SPSS for Windows (Release 11; SPSS Inc.). The main analyses were two 4 x 2 x 2 within group ANOVA's, which considered the effect of level of difficulty of the n-back task (i.e. 0-, 1-, 2-, or 3-back), medication status (i.e. medication-free vs. post-medication), and imaging session (i.e. scanning session 1 vs. scanning session 2), on both accuracy (i.e. mean percentage correct) and reaction time.

Independent samples t-tests were conducted to compare the performance of participants between experimental phases (i.e. medication-free vs. post-medication), using the data acquired for each of the additional cognitive and affective assessments administered to participants at each stage.

6.4.4.2 Functional Imaging Data

All functional data were processed and analysed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm/). With respect to the preprocessing of functional imaging data, the same realignment, normalisation and smoothing parameters as were employed in experiment two were used here (see pp 132-133 for details). The only notable difference in the preprocessing of imaging data in experiment three was that participants' EPI images were not co-registered to their T1 structural images. Instead, they were normalised to the SPM99 EPI template image, omitting a separate co-registration step in preprocessing.

Fixed effects analyses were initially calculated for individual participants in order to determine linear increases and decreases in cortical activation in individual voxels associated with the linear increase in the level of difficulty on the n-back task. Fixed effects contrasts were also constructed for the each of the experimental conditions, i.e. medication-free and post-medication. Moreover, fixed effects analyses were conducted in order compare these experimental conditions in terms of relative differences in increases and decreases in activation associated with increasing task difficulty.

The fixed effects contrasts for each participant were also used to determine the regions of significant cortical activation in a random effects model of the functional activation associated with both of the within subjects factors of interest, i.e. level of task difficulty and experimental condition.

6.4.5.3 Examination of structural images

Although, the structural imaging data was not used for volume calculations, the T1 structural images of all participants were examined for any evidence of significant structural abnormalities.

Chapter 7: Results - Experiment Three

7.1 Results of blood sample analysis

Each participant was required to provide a blood sample prior to their post-medication scan, and after they had taken their final dose. It was ensured that the time of consumption of the last dose of medication was no longer than six hours before scanning (i.e. mean = 230 minutes, s.d. = 78.59 minutes, minimum = 115 minutes, maximum = 340 minutes).

Blood plasma separated from each sample obtained was analysed for concentration of total S-citalopram and total N-desmethylcitalopram (norcitalopram), using high-performance liquid chromatography. The results of this analysis are detailed in Table 7.1 below. All blood samples were acquired prior to scanning.

Participant Scan Number	*[S-citalopram] (μg/L)*	*[N-desmethylcitalopram] (μg/L)*
020402	20	10
069665	20	nd
295005	10	nd
331262	30	10
387931	20	10
388264	20	nd
392777	30	10
394514	20	10
394515	20	nd
394534	20	10

Table 7.1: Concentration of citalopram and desmethylcitalopram detected in blood serum samples from participants in experiment three. (Note: nd = not detected, concentration below limit of accurate measurement of 10 μg/L).

7.2 Behavioural Results

7.2.1 Affective Assessments

Paired samples t-tests on each of the affective measures revealed that medication had no effect on mean BDI score (i.e. $t_{(9)} = -1.60$, $p = 0.145$), mean stress score (i.e. $t_{(9)} = 1.08$, $p = 0.155$), nor mean arousal score (i.e. $t_{(9)} = -0.36$, $p = 0.365$). However, there was a significant difference between medication-free and post-medication scores on the APSAQ (i.e. $t_{(9)} = -2.17$, $p = 0.029$).

	Medication Free		*Post Medication*		*Paired Difference: Mean (s.d)*
	Mean (s.d.)	Min-Max	Mean (s.d.)	Min-Max	
BDI	2.00 (2.91)	0 – 9	3.60 (3.307)	0 – 10	-1.60(3.17)
SAC – Stress	7.70 (1.06)	5 – 9	7.30 (1.494)	5 – 9	.40(1.17)
SAC – Arousal	6.00 (2.16)	1 – 9	6.30 (1.889)	3 –10	-.30(2.67)
APSAQ	16.50 (3.03)	12 – 22	19.30 (3.173)	13 – 24	-2.80(4.08)

Table 7.2: Mean scores and distribution of scores on each of the affective measures in experiment three: Medication free vs. post-medication

In order to determine whether these results were the result of the medication or whether there was a confounding effect of scanning session (i.e. first vs. second scan irrespective of medication status), further paired t-tests were carried out.

The results of this additional set of analyses were also indicative of no effect of scanning order on measures of depression (i.e. BDI: $t_{(9)} = 1.60$, $p = 0.145$), stress (i.e. $t_{(9)} = 0.51$, $p = 0.619$), or arousal (i.e. $t_{(9)} = -0.12$, $p = 0.909$) scores. In addition, there was no observed significant difference between the average scores for participants on the APSAQ between the first and second test sessions, irrespective of medication status (i.e. $t_{(9)} = 0.78$, $p = 0.456$).

Therefore, it can be concluded that subacute administration of escitalopram had no significant effect on the presence of depressive symptoms in participants. Similarly, escitalopram appeared to have little or no effect on the level of state stress or arousal that participants experienced on each of the testing occasions. However, the converse was found to be true for levels of state anxiety. Indeed, the consumption of escitalopram for 7 days resulted in an increase in state anxiety in participants, as indicated by the relative increase in APSAQ scores between the medication free and post-medication testing sessions. The failure to find a significant difference in the average APSAQ scores between first and second scanning trials, without regarding medication status, indicates that the increase in anxiety in attributable to the administration of medication, rather than an effect of repeat testing.

7.2.2 Test of Everyday Attention

Additional paired samples t-tests were carried out in order to compare the relative performance of participants in the medication-free and post-medication experimental conditions on each of the measures of TEA subtests used in this study.

7.2.2.1 Elevator counting with distraction

The administration of escitalopram had no effect on the performance of participants on the elevator counting with distraction task. This was true for both the raw and scaled accuracy scores on this measure (i.e. $t_{(9)} = -0.56$, $p = 0.591$ and $t_{(9)} = -0.74$, $p = 0.479$, respectively).

7.2.2.2 Visual elevator

7.2.2.2.1 Accuracy

As with the elevator counting with distraction task, there were no significant differences in participant performance in medication-free and post-medication conditions on the accuracy measure on the visual elevator subtest. Again, this was observed in the analysis of both raw and scaled score (i.e. $t_{(9)} = 0$, $p = 1.00$ and $t_{(9)} = 0.568$, $p = 0.584$, respectively).

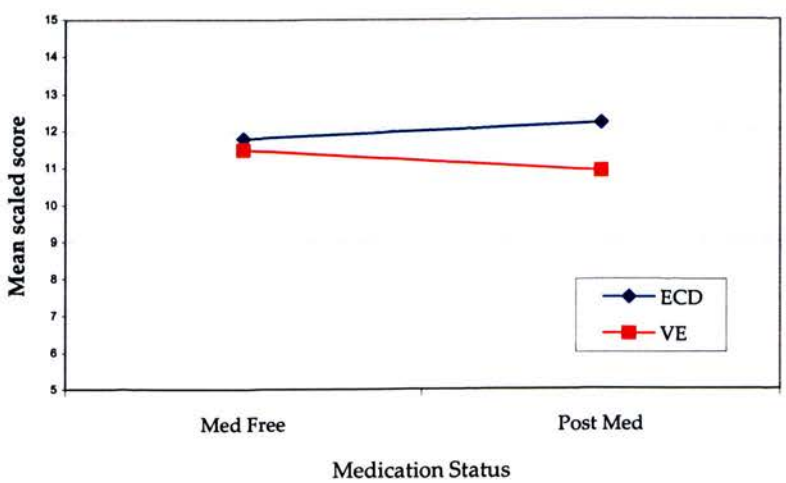

Figure 7.1: Comparison of mean scaled scores for the elevator counting with distraction and visual elevator tasks – Experiment three: Medication free vs. post-medication condition.

7.2.2.2.2 Timing

Similarly, the experimental manipulation of medication status did not have a significant effect on the timing score on the visual elevator task. A series of t-test analyses revealed no

significant difference between conditions in the mean time (in seconds) per attentional switch (i.e. $t_{(9)} = -0.963$, $p = 0.361$), nor in the mean scaled score for reaction time (i.e. $t_{(9)} = 0.745$, $p = 0.475$).

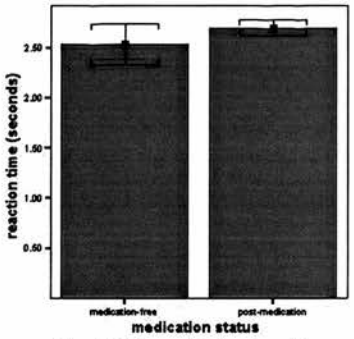

Figure 7.2: Mean reaction time (seconds) per attentional switch on the visual elevator task - Experiment three: Medicaion-free vs. post-medication conditions (i.e. N= 10)

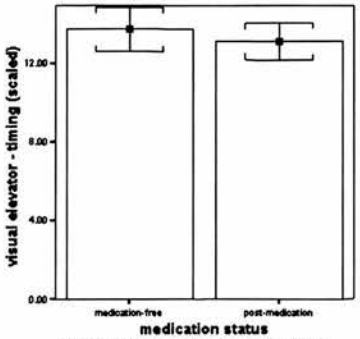

Figure 7.3: Mean scaled score on the visual elevator task - Experiment three: Medication-free vs. pos-medication condiions (i.e. N = 10)

To determine that there was no confounding effect of the order of testing session on the outcomes of the previous statistical analyses, first and second session scores for each of the TEA subtests were compared for differences in mean score, irrespective of medication status.

The results of these paired samples t-tests were indicative of no significant difference between first and second scanning sessions on the accuracy measures on both the elevator counting with distraction and visual elevator tasks, i.e. for raw and scaled scores.

While there was evidence of a significant difference between the first and second test sessions for the raw timing score on the visual elevator task (i.e. $t_{(9)} = 4.147$, $p = 0.002$), the comparison of scaled timing scores was non-significant.

Therefore, it may be concluded that the administration of escitalopram to normal healthy volunteers had no significant effect upon the cognitive performance of participants on measures of selective attention, cognitive flexibility, and auditory verbal working memory. Although there was an indication that there may have been an order effect of testing session on the psychomotor function of participants, based on observed differences in raw timing scores, analysis of the scaled scores revealed no difference. Thus, suggesting that the

psychomotor performance of participants was consistent between experimental conditions, and between first and second test sessions, irrespective of medication status.

7.2.3 Rey Auditory Verbal Learning Test

The first analyses carried out on the RAVLT data were designed to ascertain whether there was a significant difference in the mean number of items recalled on each learning trial between medication-free and post-medication conditions. The results of these analyses (i.e. paired samples t-tests) were indicative of analogous performance of participants between the experimental conditions on each of the learning trials of the RAVLT. In addition, there was no significant effect of medication status on the mean number of items recalled on the other measures on this task, i.e. interference, delayed recall, and recognition trials.

The number of items recalled is not the only measure of performance that can be derived from data obtained during performance of the RAVLT. An additional measure that is available to investigators is the effect of interference – i.e. the effect of the interference trial list on recall in the subsequent recall condition. The degree of interference experienced by participants is a further indicator of the level of difficulty experienced by participants during performance of the task. Therefore, further analyses were conducted in order to determine whether escitalopram had any significant impact on this interference effect.

The difference between scores on trial 5 and the delayed recall trial were calculated for each participant, for medication-free and post-medication test sessions. A paired samples t-test was then conducted to determine whether there was any significant difference between experimental conditions. However, the results of this analysis were indicative of no significant difference in interference in the different experimental conditions (i.e. $t_{(9)} = 0.10$, $p = 0.924$).

As with the other measures, a series of paired samples t-tests were carried out to determine whether there was any significant effect of test session on participants' scores on the RAVLT, irrespective of medication status. While there were no significant differences observed between first and second session test scores for the five learning trials on the RAVLT, there was a significant difference in the number of correctly recalled items between the first and second sessions on the delayed recall and recognition trails (i.e. $t_{(9)} = 3.431$, $p = 0.008$ and $t_{(9)}$

= 2.433, p = 0.038, respectively). In both instances the number of items correctly recalled was greater in the first test session. However, if we correct for multiple comparisons, using a Bonferroni correction, then this latter significant finding should be deemed non-significant. Thus, indicating that the only significant effect of test session is on the mean number of items correctly recalled in the delay recall trial of the RAVLT.

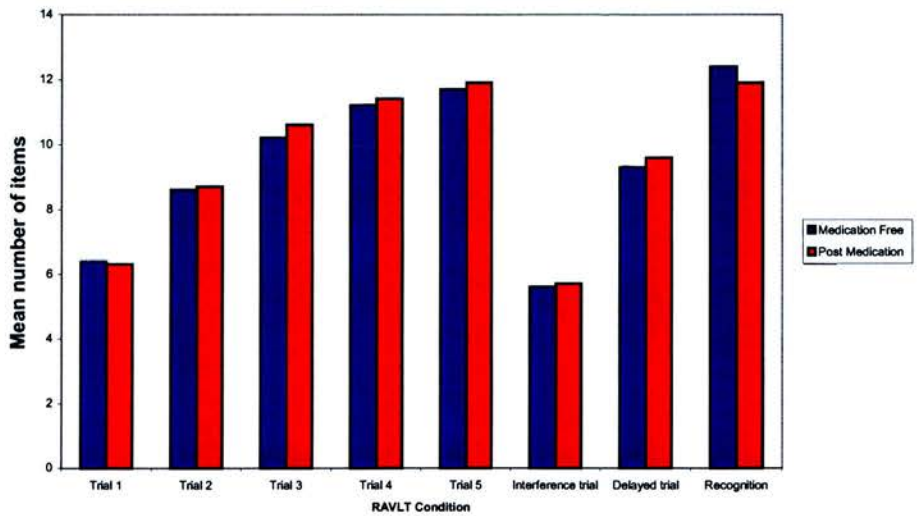

Figure 7.4: Mean number of items correctly recalled at each stage of the RAVLT task – Experiment three: Medication free vs. post-medication test conditions (i.e. N = 10).

Therefore, while it would appear that the course of escitalopram taken by the participants had no effect on either verbal learning or on interference, it does seem that there was an effect of session on the delayed recall of verbal material. However, rather than exhibiting a positive practice effect with repeated testing, participants performance on the levels of the task that tested retention of items was impaired by repeated exposure to this test.

7.2.4 n-back task

In order to establish the effect of medication status on performance on the n-back task (i.e. both accuracy and reaction time) two 2 x 2 x 4 (i.e. medication status, scan session, and level of n-back) within-subject ANOVAs were carried out.

7.2.4.1 Accuracy

Although there was further evidence in this experiment of the significant main effect of the level of difficulty of the n-back task (i.e. $F_{(1.475,\ 13.274)} = 8.260$, $p = 0.008$), the initial ANOVA analysis revealed no significant main effect of medication status on performance accuracy on

the n-back task (i.e. $F_{(1,9)} = 0.02$, $p = 0.808$). Moreover, there was no significant main effect of scanning session (i.e. $F_{(1,9)} = 0.69$, $p = 0.428$), and no significant interactions between any of the factors of interest.

With regards to within-subjects contrasts, there was a significant linear contrast associated with the level of difficulty of n-back (i.e. $F_{(1,9)} = 12.32$, $p = 0.007$). Furthermore, the reverse Helmert contrasts between 1- and 0-back, 2- and 1-back, and 3- and 2-back levels of task difficulty were all statistically significant (i.e. $F_{(1,9)} = 5.25$, $p = 0.048$, $F_{(1,9)} = 11.02$, $p = 0.009$, $F_{(1,9)} = 8.44$, $p = 0.017$). All other within-subjects contrasts failed to reach statistical significance.

Post-hoc paired sample t-tests revealed a significant difference between mean performance between 0- and 1-back levels of the task (i.e. $t_{(9)} = 2.29$, $p = 0.024$) and between the 2- and 3-back task levels (i.e. $t_{(9)} = 2.46$, $p = 0.018$), but no significant difference between the performance outcomes of participants on the 1- and 2-back task levels (i.e. $t_{(9)} = 1.50$, $p = 0.0845$). However, if we correct for multiple comparisons using the Bonferroni method of correction, then all post-hoc findings associated with accuracy outcomes between the levels of n-back fail to reach significance.

7.2.4.2 Reaction time

The second within subjects ANOVA for performance on the n-back task (i.e. reaction time) was also indicative of no significant main effect of medication status (i.e. $F_{(1,9)} = 0.09$, $p = 0.766$). On the other hand, there was a significant main effect of the level of n-back (i.e. $F_{(1.726, 15.538)} = 48.67$, $p < 0.001$) and a significant main effect of scanning session (i.e. $F_{(1,9)} = 9.47$, $p = 0.013$). Moreover, the interaction between these two factors was also significant (i.e. $F_{(3,27)} = 6.83$, $p = 0.001$).

Significant linear contrasts were noted for session (i.e. $F_{(1,9)} = 9.47$, $p = 0.013$), level of n-back (i.e. $F_{(1,9)} = 73.61$, $p < 0.001$), and for the interaction between these factors (i.e. $F_{(1,9)} = 16.29$, $p = 0.003$). There was also a significant quadratic contrast for the level of n-back (i.e. $F_{(1,9)} = 19.35$, $p = 0.002$) and significant reverse Helmert contrasts between 1- and 0-back (i.e. $F_{(1,9)} = 32.89$, $p < 0.001$), between 2- and 1-back (i.e. $F_{(1,9)} = 52.98$, $p < 0.001$) and between 3- and 2-back (i.e. $F_{(1,9)} = 77.50$, $p < 0.001$).

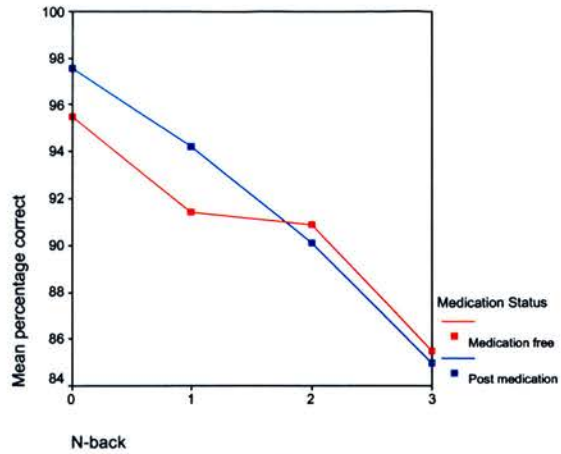

Figure 7.5: Mean percentage correct at each level of n-back – Experiment three: Medication free vs. post medication conditions (i.e. N = 10)

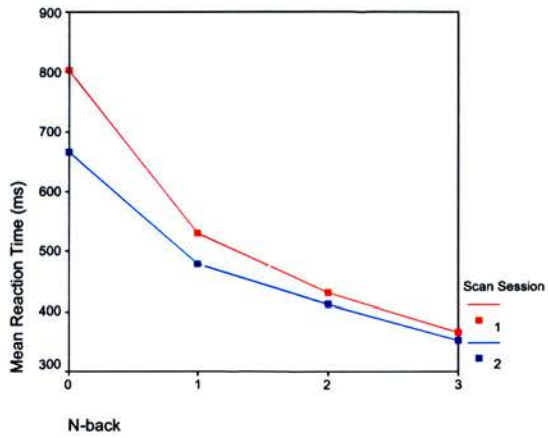

Figure 7.6: Mean reaction time (ms) at each level of n-back - Experiment three: Scanning session 1 vs. session 2.

In order to determine the nature of these significant effects, the mean reaction time for session 1 and session 2 across both scans was calculated, and a series of paired samples t-tests were carried out.

A significant difference between the mean reaction times for 0-back between session 1 and session 2 was noted (i.e. $t_{(9)} = 4.74$, $p = 0.001$). It was found that participants' reaction times for 0-back stimulus items in session 2 were quicker than in session 1. Nonetheless, there was no significant difference noted between sessions 1 and 2 for the other levels of n-back.

Paired samples t-tests were also conducted to compare the mean reaction time for each level of n-back, irrespective of medication status and scanning session. Significant differences were observed in mean reaction time between 0- and 1-back (i.e. $t_{(9)} = 5.74$, $p < 0.001$), between 1- and 2-back (i.e. $t_{(9)} = 3.20$, $p = 0.011$), and between 2- and 3-back (i.e. $t_{(9)} = 5.80$, $p < 0.001$). These results were still statistically significant after correction for multiple comparisons (i.e. Bonferroni).

In order to determine whether there was any effect of test session, irrespective of medication status, two 2 x 4 within-subject ANOVAs were carried out, in which the factors of interest were scanning session (session 1 vs. session 2) and level of n-back. As with the main ANOVA analyses, one analysis considered the effect upon percentage correct, while the other looked at reaction time.

These analyses revealed a significant main effect level of n-back on both accuracy (i.e. $F_{(3,27)} = 11.62$, $p < 0.001$) and reaction time (i.e. $F_{(1.779, 16.012)} = 53.86$, $p < 0.001$). However, there was no significant main effect of test session, and no interaction between these two factors.

With regards to the main factor of interest in this study (i.e. medication status), it can be concluded that the consumption of escitalopram had no significant effect on either the accuracy or reaction times of participants on the n-back task. Therefore, implying that the subacute administration of SSRI medication had no impact upon the integrity of working memory function in a sample of normal healthy adults.

However, the level of difficulty of the n-back task had a significant effect on both accuracy and reaction time, irrespective of medication status or scanning session. More specifically, participant's accuracy declined between the baseline level of the task (i.e. 0-back) and the first of the working memory levels of the task, and between 2- and 3-back levels. This decline in mean percentage correct was accompanied by a relative decrease in reaction time. Thus, implying an inverse relationship between perceived difficulty and psychomotor performance, i.e. as the task got more difficult participants reactions to stimulus items were faster.

7.2.5 Correlations with cognitive performance

7.2.5.1 Medication-free condition

Although there was no evidence of affective abnormality in the participants in either experimental phase, with the exception of state anxiety, analyses were conducted in order to determine whether there was any relationship between the affective state of participants in the medication-free condition and performance on the various cognitive tasks.

The results of a series of bivariate correlations revealed that the only significant associations between affect and cognitive performance in this study were a significant positive correlation between score on the APSAQ and percentage correct on the 3-back level of the n-back task (i.e. $r = 0.73$, $p = 0.016$), and between BDI score and number of items correctly identified on the 'delayed recall' and 'recognition' levels of the RAVLT (i.e. $r = 0.67$, $p = 0.034$ and $r = 0.67$, $p = 0.036$, respectively). All other correlations failed to reach significance.

7.2.5.2 Post-medication condition

A similar series of correlations were conducted to compare the same measures in the post-medication condition. Moreover, the concentration of citalopram as measured from the blood plasma of participants was also included in these analyses.

Significant positive correlations were noted between post-medication BDI and number of items correctly recalled on the second, third, fourth, and interference recall conditions of the RAVLT (i.e. $r = 0.80$, $p = 0.006$; $r = 0.75$, $p = 0.013$; $r = 0.72$, $p = 0.020$; and $r = 0.76$, $p = 0.011$, respectively), and between APSAQ score and the number of items correctly recalled on the third and fourth recall conditions of the RAVLT (i.e. $r = 0.77$, $p = 0.009$ and $r = 0.73$, $p < 0.016$). All other correlations between affective measures and cognitive performance in the post-medication condition failed to reach statistical significance.

7.3 Structural imaging results

Examination of the structural scans (i.e. T1 weighted EPI) revealed no significant abnormalities in any of the participants in this study. Therefore, all participants were included in the analyses of the BOLD EPI functional imaging data.

7.4 Functional imaging results

As with the previous study, all data were analysed using SPM99. Following spatial transformation of the images fixed effects contrasts were calculated for each participant. Contrasts were calculated for the changes in the level of activation across the cortex associated with the linear increase in difficulty of the n-back task, i.e. block-design. Both increase and decrease contrasts were calculated.

Random effects contrasts were calculated using the individual fixed effects contrasts. More specifically, contrasts were calculated for the mean increases and decreases in activation with the parametric increase in the level of difficulty of n-back for both within and between conditions (i.e. independent sample t-test and ANOVA, respectively).

Significant clusters of activation were defined as those with a corrected probability level of less than or equal to 0.05. Following identification of the significant clusters of activation the co-ordinates of the local maxima of activation were converted from MNI to Talairach stereotactic space, i.e. using the same non-linear transformation as in the previous experiment. The neuroanatomical descriptions of the locations of the significant clusters were determined using the Talairach Daemon Database.

The following sections summarise the outcomes of the imaging analysis pertaining to those regions showing alterations in the level of activation with the increase in difficulty of n-back in the medication-free and post-medication conditions, and the relevant differences between conditions. However, full details of the results of the functional imaging data in this study can be viewed in Appendices 3C and 3D.

7.4.1 Pattern of activation observed during performance of the n-back task: Medication-free

With the linear increase in difficulty in the n-back task significant increases were noted in a number of regions of cortex (see Figure 7.7). A significant cluster of increased activation was observed in the left hemisphere in a region comprising both superior and inferior parietal lobes (BA7/40; K_E/vol. = 3064/24512 mm^3, $p < 0.001$). In addition, a significant increase was seen in bilateral activation in the middle and superior frontal gyri (BA6, 46 & 8; K_E/vol. = 728/5824 mm^3, $p < 0.001$; K_E/vol. = 583/4662 mm^3, $p < 0.001$; K_E/vol. = 622/4976 mm^3, $p < 0.001$;

and K_E/vol. = 118/944 mm^3, p = 0.013) and in the right cerebellum (i.e. pyramis; K_E /vol.= 189/1512 mm^3, p = 0.001).

Significant decreases were noted in medication-free participants in the left hemisphere in the middle and inferior frontal gyri (BA11; K_E/vol. = 92/736 mm^3, p = 0.04), the superior frontal gyrus (BA8; K_E/vol. = 478/3824 mm^3, p < 0.001 and K_E/vol. = 102/816 mm^3, p = 0.026), the angular and middle temporal gyri (BA39/21; K_E/vol. = 206/1648 mm^3, p < 0.001), and in an additional cluster of activation comprising the claustrum and the superior temporal gyrus (BA 22/21; K_E/vol. = 498/3984 mm^3, p < 0.001). Significant decreases were also seen in the right pre- and postcentral gyri (BA4; K_E/vol. = 142/1136 mm^3, p = 0.005), cerebellum (i.e. culmen; K_E/vol. = 122/976 mm^3, p = 0.011), and in the parahippocampal and superior temporal gyri (BA35/38; K_E/vol. = 1057/8456 mm^3, p < 0.001). In addition, in the medication-free condition there were a number of significant decreases in a number of inter-hemispheric clusters. The local maxima of these clusters were as follows: lingual gyrus (BA18; K_E/vol. = 2835/22680 mm^3, p < 0.001), middle occipital gyrus (BA18; K_E/vol. = 859/6872 mm^3, p < 0.001), and the medial frontal gyrus (BA6; K_E/vol. = 910/7280 mm^3, p < 0.001).

7.4.2 Pattern of activation observed during performance of the n-back task: Post-medication

Following the subacute administration of escitalopram, significant increases in activation were noted the left hemisphere increased in the insula (BA43/52; K_E/vol. = 256/2048 mm^3, p < 0.001) and in a cluster involving the inferior and superior parietal lobules and the precuneus (BA7; K_E/vol. = 3767/30136 mm^3, p < 0.001). Significant increases were also seen in the right hemisphere in the insula and inferior and middle frontal gyri (BA43/52/47,9, & 6; K_E/vol. = 205/1640 mm^3, p < 0.001; K_E/vol. = 62/496 mm^3, p = 0.054; and K_E/vol. = 556/4448 mm^3, p < 0.001), and in two interhemisphic clusters – i.e. both comprising the superior and middle frontal gyri (BA 10 & 6; K_E/vol. = 333/2664 mm^3, p < 0.001 and K_E/vol. = 844/6752 mm^3, p < 0.001).

Conversely, significant decreases in activation with increasing level of difficulty of n-back were found in the left hemisphere in the middle temporal and angular gyri (BA39; K_E/vol. = 242/1936 mm^3, p < 0.001), the lingual gyrus (BA18; K_E/vol. = 64/512 mm^3, p = 0.048), and the hippocampus (K_E/vol. = 172/1376 mm^3, p < 0.001). A significant decrease was also observed

in the right hemisphere in cingulate gyrus (BA24; K_E/vol. = 102/816 mm^3, p = 0.004). As with the clusters of increased activation, decreased activation was noted in interhemispheric clusters, i.e. in the superior frontal gyrus (BA8; K_E/vol. = 1779/14232 mm^3, p < 0.001), the cuneus (BA18/19; K_E/vol. = 233/1864 mm^3, p < 0.001), and the cingulate gyrus (BA24/31; K_E/vol. = 2016/16128 mm^3, p < 0.001).

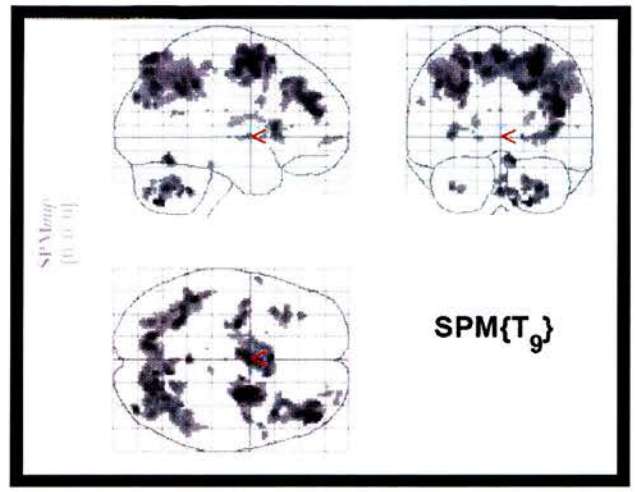

Figure 7.7: Statistical parametric map of voxels of increase activation associated with the linear increase in difficulty of the n-back task in the medication-free condition – Experiment three: Random effects.

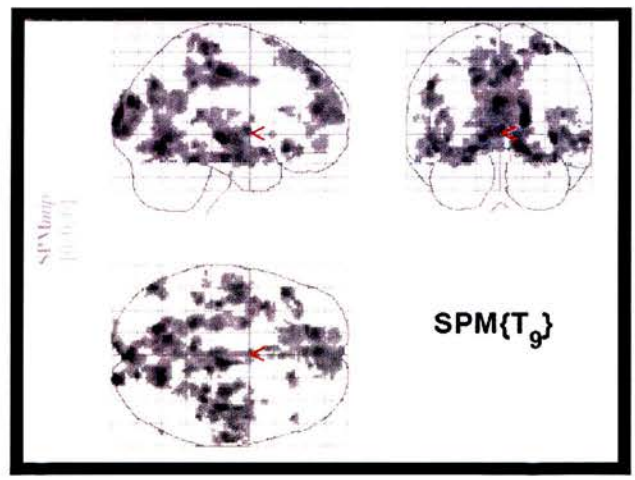

Figure 7.8: Statistical parametric map of voxels of decreased activation associated with the linear increase in difficulty of the n-back task in the medication-free condition – Experiment three: Random effects.

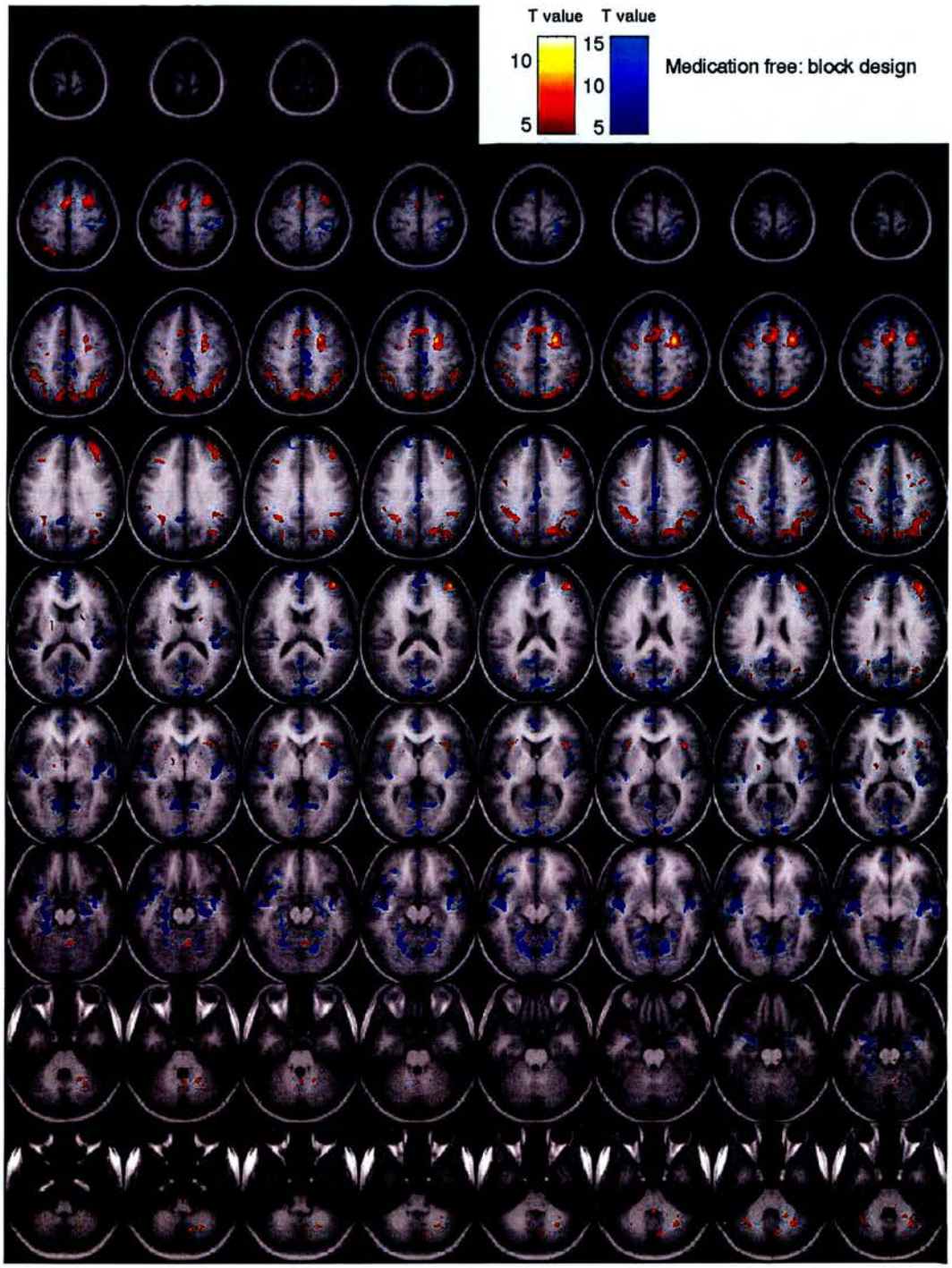

Figure 7.9: Increased (red colour scale) and decreased (blue colour scale) activation associated with the linear increase in difficulty of the n-back task in the medication-free condition – Experiment three: Random effects. The patterns of activation have been superimposed on a normalised, mean EPI image (details as before).

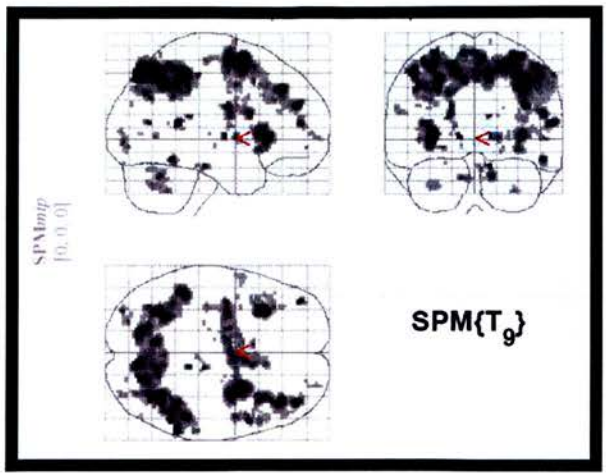

Figure 7.10: Statistical parametric map of voxels of increased activation associated with the linear increase in difficulty of the n-back task during the post-medication condition – Experiment three: Random effects.

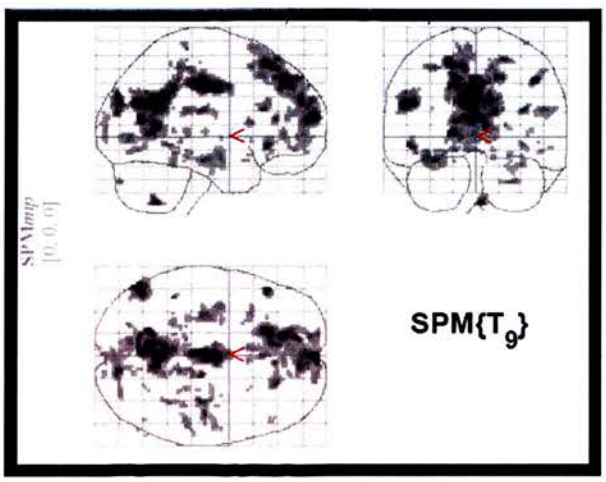

Figure 7.11: Statistical parametric map of voxels of decrease activation associated with the linear increase in difficulty of the n-back task in the post-medication condition: Random effects.

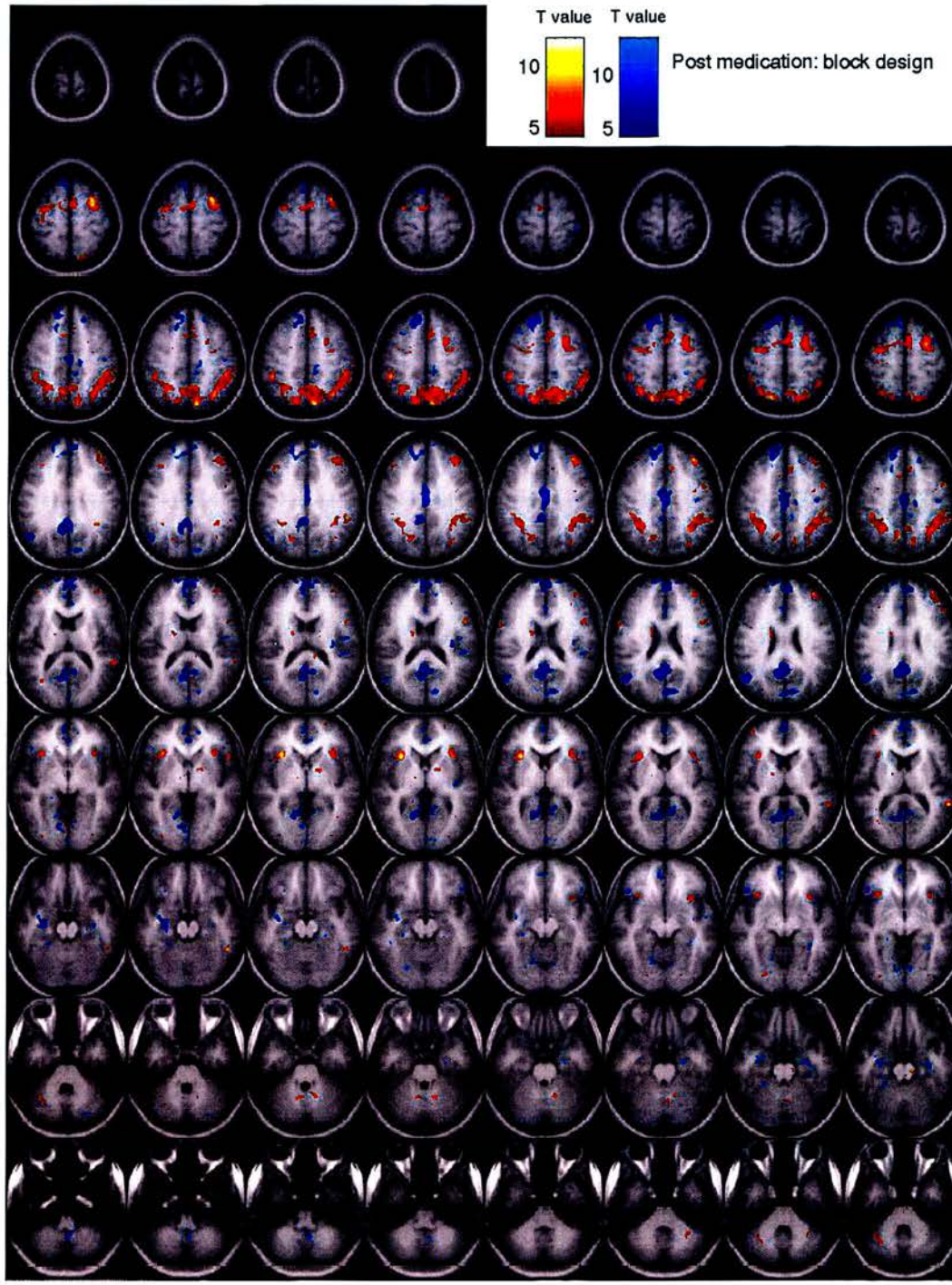

Figure 7.12: Increased (red colour scale) and decreased (blue colour scale) associated with the linear increase in difficulty of the n-back task during the post-medication condition – Experiment three: Random effects. The patterns of activation have been superimposed on a normalised, mean EPI image (details as before).

7.4.3 Comparison of the observed pattern of activation between medication free and post-medication conditions

The random effects contrasts for the comparison of relative activation between the medication-free and post-medication conditions revealed no clusters of statistically significant different activation (see Figures 7.15 and 7.16). Yet, despite the lack of significant random effects, the fixed contrasts revealed clusters of activation that were significantly different between the two experimental conditions (see Appendix 3A for full details). Given that participants acted as their own controls it is likely that the fixed effected differences between conditions may reflect genuine medication related effects on cortical activation, but which are effected by the reduced statistical power resulting from the use of a relatively small sample, and by the increased conservativeness of the random effects analysis.

In the fixed effects contrasts, a significant increase was seen in gray matter in the left hemisphere in a cluster which involved anterior cingulate and middle frontal gyrus (BA24; K_E/vol. = 280/2240 mm^3, $p = 0.008$) – i.e. the level of activation in this region was relatively more increased in participants in the medication-free condition compared to the post-medication condition.

Conversely, a statistically significant relative decrease in the medication-free condition was observed in the left middle occipital gyrus (BA19; K_E/vol. = 195/1560 mm^3, $p = 0.040$), the right superior temporal gyrus (BA42; K_E/vol. = 442/3536 mm^3, $p < 0.001$), and the right cerebellum (K_E/vol. = 212/1696 mm^3, $p = 0.029$).

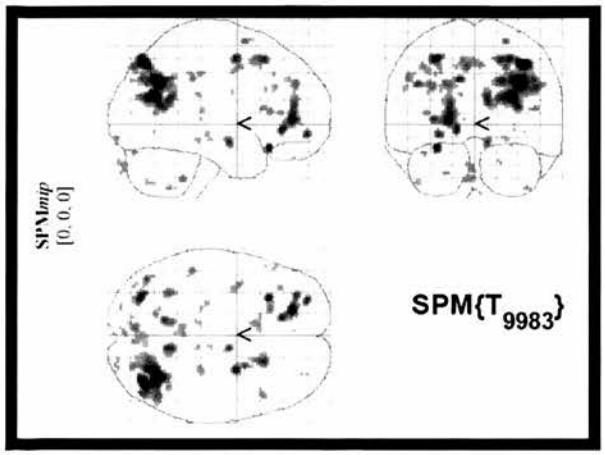

Figure 7.13: Statistical parametric map of the voxels of relatively increased activation in the medication-free compared the post-medication condition, i.e. associated with the linear increase in difficulty of the n-back task – Experiment three: Fixed effects.

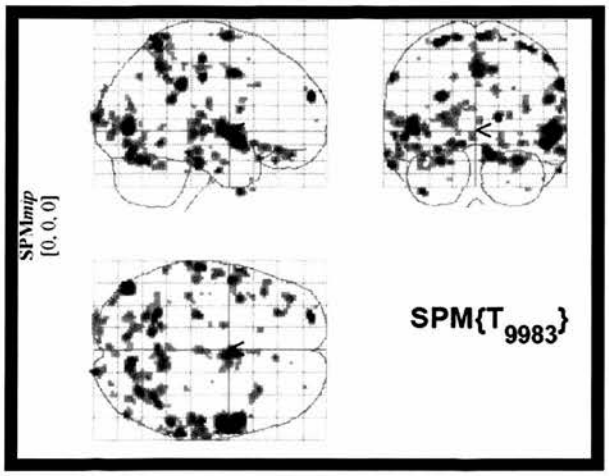

Figure 7.14: Statistical parametric map of the voxels of relatively decreased activation in the medication-free compared to the post-medication condition, i.e. associated with the linear increase in difficulty of the n-back task - Experiment three: Fixed effects.

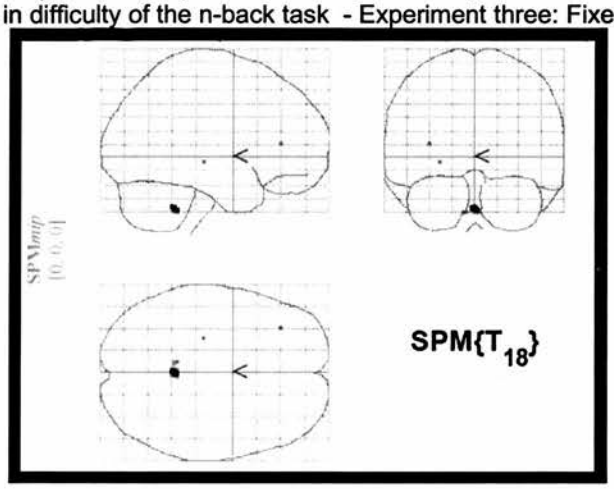

Figure 7.15: Statistical parametric map of voxels of relative increase in the medication-free condition compared to the post-medication condition, i.e. associated with the linear increase in difficulty of the n-back task – Experiment three: Random effects.

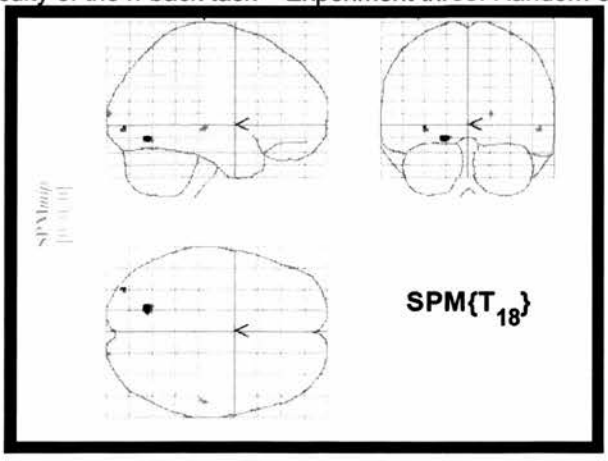

Figure 7.16: Statistical parametric map of voxels of relative decrease in the medication-free condition compared to the post-medication condition, i.e. associated with the linear increase in difficulty of the n-back task – Experiment three: Random effects.

Additional analyses were conducted to aid the interpretation of the data outlined about. In order to determine whether any effect observed between the two experimental conditions was genuinely due to the effect of medication a random effects contrast was calculated whereby participants first scan was compared with their second scan irrespective of medication status. Furthermore, we sought to establish whether the failure to observe any significant effects in the random effects comparison was the result of outliers in the data. In order to achieve this an image was created for each participant that was equal to the difference in activation between the medication-free and post-medication images for the changes in activation associated with the parametric increase in difficulty of n-back. These images were then utilised to calculate a one-sample t-test for the mean difference in levels of activation between the two conditions, rather than comparing the means of the two conditions, which would be readily distorted by outliers in the data set. Both of these analyses revealed no statistically significant clusters of activation.

Therefore, the outcomes of the analyses of functional imaging data are indicative of a reliable activation in areas cortex previously identified as being sensitive to manipulations in working memory task, including a number of frontal and parietal regions. However, there does not appear to be any significant effect of the subacute administration of escitalopram on metabolic activity, as measured using BOLD fMRI, during performance of the parametric working memory task. Nonetheless, the results of the fixed effects comparisons of participants in the medication-free and post-medication conditions does indicate a potential medication mediated effect on activation in the anterior cingulate, as well as more posterior cortical regions.

Chapter 8: Summary, discussion, and conclusions

8.1 Summary of experimental findings

The first section of this chapter will review and summarise the key observations from the series of investigations that comprised this project. Given the volume of data resulting from these studies, the outcomes of each separate study will initially be considered independently of the others.

8.1.1 Experiment one

The main aim of the first experiment was to determine whether individuals with a diagnosis of major depression would experience a deficit in working memory function, in comparison to a sample of matched healthy controls. In addition, this study was also concerned with the performance of depressed patients and normal controls on other measures of executive function, including assessments of cognitive flexibility and selective attention.

Experimental limitations

Although both the HRSD and the BDI assessments were indicative of a significant level of current depression in the patient sample in this study, it is important to recognise the limitations imposed by not employing a structured diagnostic interview in order to establish the psychiatric profile of patients. The reliance on the diagnosis of individual physicians may have confounded the outcomes due to the possibility of individual differences in diagnosis, and even the possibility of misdiagnosis. The use of a diagnostic interview may have been useful in ensuring the reliability of the assertion that patients were indeed suffering from MDD and may have aided in establishing the psychiatric homogeneity of the patient sample.

In comparison to a number of previous investigations the patients who participated in this study were relatively young, and on average appeared to be suffering from chronic depression (i.e. the average length of current depressive episode = 13.9 months). Given the potential limitations imposed by each of these factors, it is important to bear both of these factors in mind when interpreting the outcomes of this investigation. Previous investigations are indicative of a qualitative difference in the cognitive profile of different age-based cohorts of depressed patients (e.g. Elliott, 1998). Similarly, there is the possibility

of significant differences in the cognitive presentation of depressed patients based on the duration and severity of illness (see section 1.1 for a review).

The lengthy duration of depressive episode and the relatively young age of participants may be indicative of a comparatively young age of onset of first episode of depression in the patients who took part in this study, which may also have had a significant impact on the pattern of neuropsychological function noted in this group. The relevant background literature does support the notion of a significant relationship between the age of onset and performance on measures of executive function (i.e. Grant et al., 2001), thus making this of particular concern in the interpretation of the findings of this study.

While both of these factors do not necessarily impact upon the reliability of the observations made in this investigation, it is imperative to note that the relatively young age of the patient sample and the chronic nature of their presentation may make the findings of this study specific to this sub-group of depressed patients.

Affective profile

Depressed patients who were selected to participate in the experiment one were individuals with a diagnosis of MDD. The results of the psychometric measures of depression used in this study, i.e. the BDI and the HRSD, were indicative of a significant level of depression in patients who participated in the experiment (i.e. mean score 33.25 and 23.90, respectively). Moreover, the experience of major depression in patients was associated with a significant increase in the subjective level of state stress, arousal, and anxiety (i.e. as determined by the SAC and APSAQ affective indices).

The normal psychiatric state of the healthy volunteers was determined with the use of the same affective assessments, with the exception of the HRSD. Levels of state stress, arousal, and anxiety were also significantly smaller in the controls compared to the depressed patients, and all controls scored within the 'normal' range of the BDI. Indeed, controls' scores were almost exclusively in the normal range on all affective measures.

Cognitive profile

The differences in the affective profile of the patients and controls were associated with a range of discrepancies in performance on the measures of executive function that were employed in experiment one.

Depressed patients were found to be significantly impaired in the accuracy measures of the elevator counting and visual elevator subtests of the TEA. Thus, indicating a significant depression associated dysfunction of selective attention, attentional switching, and cognitive flexibility. Moreover, the average time taken to make attentional switches on the visual elevator task was significantly increased in depressed patients, which was indicative of a degree of psychomotor slowing associated with the experience of major depression.

The primary measure of executive function in experiment one was the parametric working memory task that participants were required to undertake, i.e. the n-back task. The parametric increase in the number of items to be recalled on the n-back task resulted in the predicted increase in the perceived difficulty of the task in both patients and controls. Indeed, both post-hoc analyses and *a priori* contrasts revealed a significant decrease in performance with each incremental increase in task difficulty in both experimental groups. The effect of the level of difficulty of n-back was evident not only in the significant main effect of n-back on the mean percentage of items correctly recalled at each level of task difficulty, but also in the significant linear contrast for the effect of the parametric manipulation of cognitive load on accuracy.

With regards to the relative performance of depressed patients and healthy controls on the n-back task, there was an apparent depression associated deficit in accuracy on the n-back task. This was evident in the lower levels of the number of correct responses in patients at all levels of the task. The lack of a significant interaction between participant group and percentage of correct items at each level of n-back was suggestive of a dysfunction in working memory in depressed patients that was consistent in nature, i.e. the discrepancy in the accuracy of patients and controls did not alter disproportionately as the difficulty of the n-back task was increased.

The disparity in the performance of depressed patients and controls was also evident in participants' reaction times on the n-back task. There was a significant effect of affective status on mean reaction time at each level of n-back, which was evident in the longer reaction times of depressed patients, compared to controls, at all levels. In addition, there was also a significant interaction between participant group and level of n-back, suggesting a disproportionate effect of task difficulty on reaction time in the two experimental groups. However, post-hoc analysis indicated that this interaction effect was the result of a relative speeding up of responses in all participants between 0- and 1-back conditions of the task.

The post-hoc analysis of participants' reaction time data also aided in the interpretation of the main effect of n-back that was observed in experiment one. The analysis failed to find a statistically significant difference in the mean reaction times of all participants between the subsequent levels of the task (i.e. 1- vs. 2-back, and 2- vs. 3-back). This observation suggests that the noted main effect of n-back was the consequence of the discrepancy in reaction time between the first two levels of the task, rather than an effect of the increase in cognitive load across all tasks levels.

An important discrepancy that was identified in the profile of depressed patients and controls was a significant difference in the mean NART estimated IQ scores of the two participant groups. To determine the potential effect of this difference upon the previously observed outcomes, the analyses for the n-back data were recalculated including estimated IQ as a covariate.

The inclusion of IQ in the ANCOVA analysis did not effect the previously observed depression associated deficit in terms of accuracy on the task, but did result in a failure to observe a significant main effect of the level of difficulty of n-back. Post-hoc analysis of the data revealed that there was only a significant association between mean accuracy on the 0-back levels of the task and participant IQ, thus, suggesting that at baseline levels of the task factors that are related to IQ may play a more significant role in participant performance than aspects of executive function. All other correlations between the performance at the additional levels of N and IQ were not significant.

Further post-hoc analysis of the relative performance of participants at each level of the n-back task (i.e. one-way ANCOVAs, with IQ as a covariate) revealed that there was a significant difference between the mean accuracy of depressed patients and controls at the 1- and 2-back levels of n-back, and a trend towards a significant difference at the 3-back task level. This observation indicates that the previously noted discrepancy in the performance of patients and controls at the 0-back level of the task was confounded by factors related to participant IQ, such as psychomotor ability.

Controlling for IQ in the analysis of reaction times on the n-back task produced a similar pattern of results. The inclusion of IQ as a covariate in the analyses resulted in a failure to find a significant main effect of n-back in both participant groups. However, if we consider the findings of the previous analysis of average reaction time on the n-back task, this is apparently only a reversal of the effect of n-back on reaction time on 0-back trials. There was also a significant effect of depression on reaction time, despite controlling for IQ in this analysis, in conjunction with a significant interaction between participant group and level of difficulty of n-back. Post-hoc ANCOVAs revealed that the experience of depression had a significant effect on reaction time, resulting in differences between patients and controls on all levels of the n-back task, even after controlling for the discrepancies in the mean IQ of the two groups.

The results of these analyses suggest that participant IQ is an important mediating factor in performance of the n-back task, but only with respect to the performance accuracy of participants at the 0-back level of task difficulty. The observation of an effect at this level of the n-back task with the inclusion of IQ as a covariate of performance may be attributed to the previously documented association between elementary factors of cognitive function – such as psychomotor ability – and intelligence (e.g. Deary & Stough, 1996; Deary et al., 1997). This implies that performance on the n-back task is at least partially related to the psychomotor ability of the participant, which is in turn related to estimates of participant IQ. Despite the confounding effect of IQ on performance, the mean differences between patients and controls were not substantially affected by the inclusion of IQ as a covariate in the latter data analysis, which indicates that the differences seen in patients and controls cannot be explained by differences in psychomotor ability alone. If this were the case, then the

ANCOVA analyses would have been anticipated to fail in finding a significant main effect of participant group on measures of performance accuracy.

The final factor of consideration in the analyses of the cognitive performance of participants in experiment one was the relationship between clinical variables and performance of depressed patients on the executive measures that were used. Severity of depression (i.e. BDI) was significantly negatively correlated with the performance of participants at the 3-back level of the working memory task, thus, indicating that the relationship between severity of depression and cognitive performance may only be of importance on more difficult cognitive tasks.

The only other clinical variable that was found to have an association with cognitive performance was the time between initial diagnosis and time of assessment. Significant negative correlations were noted between this factor and the mean percentage of correct items at the 2- and 3-back levels of the task in depressed patients. Given that the patients who participated in this study were significantly depressed at the time of assessment, this finding is indicative of a relationship between chronic depressive illness and performance on working memory tasks. However, as with severity of depression, this effect seems to apply only to the more difficult levels of the task.

Therefore, the results of experiment one were indicative of an impairment of working memory function in adults with major depression. While the degree of depression associated impairment may have been partially related to a dysfunction of psychomotor ability, motor impairment was not sufficient to explain the discrepancy in the performance of depressed patients and healthy volunteers. However, the effect of the manipulation of cognitive load in the working memory paradigm that was used in this study was apparently mediated to some degree by participant intelligence. Moreover, the linear increase in cognitive load did not disproportionately affect the ability of depressed patients to perform the n-back task, which suggests that the effect of cognitive load may not have been the primary factor in the noted deficit in working memory of patients

8.1.2 Experiment two

The experimental methodology employed in experiment two was designed to ascertain if the performance of a test of working memory would be associated with a disparity in the regions of cortical activation exhibited by depressed patients and healthy volunteers. Although two sets of statistical analyses were conducted – one for all participants involved in the study, and one for those participants who were included in the analysis of functional neuroimaging results – the following summary is concerned with the general pattern of results for depressed patients and controls in the first of these analyses.

The power of this study to detect genuine differences between the depressed patients and healthy controls on behavioural measures was potentially reduced as a result of two main factors. On one hand, there was the likelihood that differences in performance on measures of executive function may be difficult to detect, or borderline for distinguishing between depressed and non-depressed individuals. In addition, the relatively small number of participants in experiment two (i.e. only ten for both experimental groups) further reduced the power of the study to detect genuine behavioural differences between patients and controls. Therefore, the determination of an accurate profile of cognitive function associated with major depression, which appropriately accounted for the performance of depressed patients in this study, is more easily obtained by the examination of the entire data set, rather than of sub-sets of data. For this reason, it is preferential to consider the results of the preliminary analysis of this data set. However, the comparison of the profile of cognitive function in the experimental groups which were observed not only between the two analyses in this investigation, but also between experiment one and experiment two outcomes, may aid the determination of those factors of cognition which are altered in depressed patients, and which may be sensitive to reduced levels of statistical power.

In the second experiment similar limiting factors relating to the patients' profile were noted as were observed in the previous study. Again, the failure to use a structured diagnostic interview, the relatively young age of participants, and the chronic duration of their depressive episodes may have impacted upon the cognitive profile of patients who participated in this study (see above for details of the potential impact of each of these factors).

Behavioural results

- Affective profile

As with the previous study, depressed patients in experiment two exhibited a significant level of depression – on both the BDI and the HRSD – in conjunction with relatively high levels of state stress and anxiety. Controls, on the other hand, were confirmed to be free of depressive symptoms, and tended to score within a more normal range for measures of stress and anxiety. This pattern of cognitive function was established in both the preliminary data analyses and the analyses of data from those participants who were included in the functional imaging analysis only.

- Cognitive profile

In contrast to experiment one, depressed patients were unimpaired on both the visual elevator and elevator counting with distraction subtests, with respect to accuracy. However, patients' reaction times on the visual elevator were significantly slower than controls. The pattern of findings was the same in the second set of analyses. Thus, suggesting that the integrity of the mechanisms of cognitive flexibility, selective attention, and attentional switching were all preserved in the sample of depressed patients who participated in experiment two, while psychomotor function was relatively impaired.

Although the analysis of the outcomes on the TEA subtests were indicative of a sparing of central executive function, and a dysfunction of psychomotor ability, the pattern of findings relating to performance on the n-back task suggested the opposite profile of impairment. Indeed, the accuracy of depressed patients was significantly reduced on the n-back task compared to controls. Yet, patients were not significantly slower than normal controls in their response times at any level of the task.

The other factors of interest in the analysis of n-back performance in this experiment were the level of difficulty of n-back and the scanning session. The level of difficulty of n-back was found to have a significant effect on the both accuracy and reaction time measures of n-back performance, across experimental groups. Post-hoc analyses revealed a relative decline in accuracy associated with each incremental increase of cognitive load. In addition, increased reaction times in participants were found to be associated with the parametric increase in cognitive load up to and including the 2-back conditions of the task.

While the use of two separate scanning sessions appeared to have no effect on the accuracy of participants on the n-back task, there was a significant interaction between the level of n-back and scanning session on reaction time measures. However, post-hoc analyses revealed that scanning session was a contributory factor only on the reaction time of participants on 0-back levels of the task. Given that the effect of scanning session is particular to the baseline level of the task, rather than applicable to all levels of the tasks, suggests that there is something specific about performance at the 0-back level that is amenable to some factor related to the scanning session. For example, it is possible that the effect of scanning session at this level of the task was the result of an increased level of stress or arousal, resulting from the rather long scanning sessions that were used in the functional imaging paradigm in this investigation.

The profile of participant performance on the n-back task was similar in the sub-group of participants who were included in the functional imaging analysis. However, the second analysis failed to find a significant main effect of participant group on accuracy on the n-back task. However, there was considerable similarity in the cognitive profile of the participants who were included in the analysis of functional imaging data and participants in experiment one. Moreover, the pattern of cognitive function in both analyses of experiment two were also similar. Thus, it is likely that the failure to find a significant effect in the behavioural analysis of participants who were included in the functional imaging analysis is related to the reduced statistical power associated with the diminished number of participants in the second experiment, rather than a lack of a genuine difference in the performance of patients and controls. However, it is important to note that the smaller number of participants in the second experiment was due to the practical considerations of conducting an fMRI investigation.

A series of correlations revealed no significant associations between clinical dimensions in the depressed group and performance on any of the measures of executive function. This may have been due to a lack of relationship between affective state and cognitive function. Alternatively, it may have been the result of homogeneity in the affective profile in the depressed group, or in a similarity in the performance of patients on each of the cognitive measures, irrespective of variability in affective factors.

- Profile of cognitive function in depression: Experiment one vs. experiment two

Effect size comparisons of the relative performance of depressed patients and healthy controls on the n-back task revealed a greater effect of depression on accuracy on the n-back task in the second study. The similarity of the profile of cognitive function in both studies supports the notion of a genuine difference between the ability of depressed patients and healthy controls to successfully undertake tasks reliant on human working memory. Moreover, this observation is indicative of reduced statistical power in the second data analysis in experiment two.

In contrast, the comparison of the effect sizes in experiments one and two revealed a greater effect of experimental group on the observed reaction times of participants during performance of the n-back task in the first investigation. This difference was statistically significant in the first study, but not in the second, probably due to smaller group sizes in the latter. Despite the difference in the magnitude of effect sizes pertaining to reaction time differences between patient and controls at each level of n-back, the pattern of findings was similar in experiments one and two.

Unlike measures of accuracy, deficits in psychomotor ability in depressed individuals tend to be consistent across studies, even on those studies, and have been noted in those experiments that have used quite elementary psychomotor assessments or have tested comparatively few patients. Therefore, the failure to find a significant difference between patients and controls on this measure on the n-back task may reflect more than just reduced statistical power, as a result of relatively small group numbers. This raises the question of which factors specific to this investigation may have led to a relative speeding up of the response times of depressed patients?

All experimental factors were kept constant between experiments one and two, with the exception of the introduction of the performance of the working memory task during functional neuroimaging in the latter study. Thus, it would appear to be some factor associated with the performance of the n-back task whilst being scanned led to the observed similarity in the reaction times of depressed patients and healthy controls. One possible explanation of this finding is that increased levels of stress and arousal in either participant group impacted upon psychomotor function during scanning. Although the pre-test

measures where not indicative of such an alteration, the environment of the scanner may have induced an increased level of state stress and arousal. Such an effect could have resulted in an impairment of psychomotor performance of controls, or may have led to an arousal related reduction in the reaction times of patients. Either of these effects would bring about the reduction in the disparity in psychomotor function of patients and controls. However, in order to qualify this it would be necessary to have some measure of stress and arousal which could be conducted while participants are inside the scanner, e.g. measuring heart rate, or other physiological indicators of stress and arousal.

Functional neuroimaging results

The main analyses of the functional neuroimaging data were concerned with the regions of altered cortical activation – i.e. increased and decreased – that were associated with the parametric increase in difficulty of the n-back task in both patients and controls. The analyses were also designed to ascertain regions of cortical activation, during task performance, which were differentially activated in patients and controls. In order to account for the potential confounding effect of differences in the behavioural performance of the experimental groups, those regions that exhibited load-dependent activation associated with correct responses only on the n-back task were determined for depressed patients and healthy controls, and compared for relative differences.

The original block-design analysis of the functional imaging data revealed clusters of significantly increased activation associated with the increase in cognitive load in the control group in both hemispheres in parietal and frontal cortex – including inferior and superior parietal regions and both middle and medial frontal gyri. However, the pattern of decreased activation was much more diffuse in controls, comprising regions in both hemispheres and across the cortex – including parietal (i.e. posterior cingulate cortex), frontal (i.e. medial and middle frontal gyri), temporal (i.e. superior and middle temporal, parahippocampal, precentral, and fusiform gyri, and insula), and occipital regions (i.e. middle occipital and lingual gyri, and the cuneus). The relative specificity of regions of increased activation, in comparison to the diffuse pattern of decreased activation, in response to the increased difficulty of the n-back task may be indicative of a selective activation of cortical regions associated with the response to cognitive load in controls, and a corresponding decrease in cortical areas not necessary for the response to such experimental manipulations.

The regions of increased activation in patients associated with the increase in the level of n-back also included regions of the frontal and parietal cortex, such as the inferior, middle and superior frontal gyri, and the inferior parietal lobule, but also included clusters of significant activation in both the cerebellum and the lingual gyrus. The analysis of functional imaging data also revealed significant decreases in activation in patients in a number of cortical regions. As with controls, decreased activation associated with increased task difficulty occurred in parietal (i.e. posterior cingulate cortex), frontal (i.e. medial frontal gyrus), and temporal (i.e. transverse, superior and middle temporal gyri) regions. Moreover, clusters of decreased activation in depressed patients were noted bilaterally in the cerebellum. Thus, the pattern of activation in depressed patients was also suggestive of a relatively specific pattern of altered cortical activation in response to task demands.

Although the analysis of the experimental groups independently was indicative of differences in the level of activation in a number of regions between patients and controls, the statistical analysis of the alteration in cerebral activation in the experimental groups revealed relatively few differences between patients and controls. Indeed, comparison of the regions of both increased and decreased activation associated with the increased difficulty of the n-back task in depressed patients and healthy controls revealed a statistically significant difference in the magnitude of cortical activation between the groups in one region only, i.e. the MOPFC/rAC. More specifically, it was observed that the level of activation in this region was relatively higher in the depressed patients than in controls. However, it should be noted that both groups of participants exhibited a decrease in activation in this regions that was associated with the linear increase in the difficulty of n-back, but that the magnitude of the decrease in depressed patients was smaller than that seen in controls. It has already been noted, that the behavioural differences between patients and controls in this study may have been the result in a differential response to task difficulty, thus, it is possible that MOPFC activation was associated with a motivational aspect of task performance, rather than changes in cognitive load per se.

One of the main reasons for employing an fMRI paradigm in this study was to determine regions of abnormal cortical activation that were associated with behavioural dysfunctions in individuals with major depression. Therefore, the assumption could be made that the differences in the level of activation of the MOPFC may have been a critical factor in the

observed disparity in the accuracy of patients and controls performance on the n-back task. To determine whether this was indeed the case, the second series of analyses of the functional imaging data concentrated on the activity associated with accurate performance only in both experimental groups.

The pattern of activation seen in the secondary event-related analysis of functional imaging data was very similar to that which was noted in the initial block-design analysis. The event-related analysis of correct responses only in control participants associated with the linear increase in difficulty of the n-back task revealed significant increases in activation in the inferior and middle frontal gyri, the inferior parietal lobule, the superior temporal gyrus, the thalamus, the insula, and the cerebellum. Decreased activation in control participants was also noted in a number of regions across the cortex – including frontal (i.e. medial and superior frontal gyri, and anterior cingulate), parietal (i.e. posterior cingulate, and paracentral lobule), and temporal (i.e. superior and middle temporal, parahippocampal, and fusiform gyri, and the insula) regions.

In depressed patients, increased activation associated with the increased level of difficulty in correct responses only, was noted in the following regions: inferior parietal lobule; the middle and medial frontal gyri; the precuneus, pre- and postcentral gyri; the middle temporal gyrus; the insula; and the cerebellum. The increased activation in these regions co-occurred with a relative decrease in activation, associated with correct responses only and with increasing task difficulty, in diffuse cortical regions. Regions of significantly decreased activation were noted in the frontal (i.e. inferior, medial and superior frontal, subcallosal, and precentral gyri), parietal (i.e. paracentral lobule), occipital (i.e. cuneus, precuneus, and lingual gyrus), and temporal (i.e. insula and middle temporal gyrus) cortices, as well as the cerebellum.

As with the previous block-design analysis of the functional neuroimaging data, in the event-related analysis of correct responses there was considerable overlap between depressed patients and healthy controls for regions of increased and decreased activation associated with the linear increase in task difficulty. However, in contrast to the previous block-design findings, the results of the comparison of the pattern of activation between patients and controls in the event-related analysis revealed no statistically significant

clusters of either relatively increased or decreased activation between experimental groups. This indicates that the network of cortical regions which respond to changes in cognitive load is the same in both depressed patients and healthy controls, in those instances when participants are responding accurately.

All factors relating to the data analysis in the block-design and event-related analyses were identical, with the exception of the inclusion of data pertaining to cortical activation associated with incorrect responses in the block-design analysis. Therefore, it is possible that any differences in the cortical activation of patients and controls, which were highlighted in the block-design analysis, can be attributed to the relative weakness in the performance of patients on the n-back task. Thus, the failure of depressed patients to appropriately decrease activation in the MOPFC in response to increased task demands may be critically related to an aspect of task difficulty in measures of working memory that is specifically associated with major depression.

An important finding in both the block-design and event-related analyses of the functional imaging data in experiment two was the observation that specific neuroanatomical regions, such as the medial prefrontal cortex, comprised areas of both increased and decreased activation. This co-localisation of clusters of increased and decreased activation in single regions of cortex in response to the increase in cognitive load was noted both in depressed patients and normal controls. A number of the anatomical regions that were noted to exhibit clusters of both increased and decreased activation were regions that have previously been noted to be critical for working memory in normal healthy adults. For example, regions in frontal cortex which constitute the DLPFC, such as the medial and superior frontal gyri, and parietal regions, such as the inferior parietal lobule, demonstrated both increased and decreased responses in cortical activation in response to the increase in task difficulty.

The final factor of interest in the analysis of functional neuroimaging data in experiment two was the association between the severity of depression patients - as determined using the HRSD – and regions of altered cortical activation during performance of the n-back task. The results of a correlation analysis between level of activation in areas of increased and decreased activity associated with the linear increase in the difficulty of the n-back task and

severity of depression revealed no significant associations between these two variables. This may represent a reasonable level of homogeneity in the affective measures of the depressed patients who participated in this study, which is evident in the relatively small standard deviation of patient scores on the HRSD (i.e. s.d. = 5.55). Alternatively, it may imply that the differences in the activation response to task difficulty noted between depressed patients and healthy controls are consistent and not amenable to variations in depressive severity. However, in order to determine this it would be essential to ascertain whether variations in cortical activation can be observed in a depressed sample that exhibit greater variability in the severity of depression. Alternatively, this could be achieved by determining whether there are relative differences in cortical activation patterns associated with executive function in samples of mildly, moderately, and severely depressed patients.

8.1.3 Experiment three

Antidepressant medication was identified as a potential confounding factor in the behavioural performance and cerebral metabolism of depressed patients in experiment two. Therefore, experiment three was designed to determine the potential contribution of antidepressant medication to both of these outcome measures. This was achieved by measuring the effect of the subacute administration of escitalopram (i.e. 10mg/day for 7 days) on the performance of normal healthy volunteers on measures of executive function and learning. In addition, participants in experiment three were also assessed for alterations in cerebral activation associated with the performance of the n-back task, in both medication-free and post-medication conditions.

Behavioural results

- Affective profile

Prior to participation, it was assured that all volunteers in experiment three scored within the normal range on the BDI. Participants were also required to undertake the BDI, along with the SAC and the APSAQ, at both experimental phases – i.e. while medication-free and post-medication. Although the administration of the course of escitalopram did result in an increase in participants' state anxiety, there was no significant effect of AD medication on level of depression, or state stress and arousal.

- Cognitive profile

The comparison of participants' scores on the elevator counting with distraction and visual elevator subtests of the TEA in the medication-free and post-medication experimental conditions revealed no significant effect of escitalopram on either of these measures. Thus, indicating that the subacute administration of an SSRI medication had no effect on the ability of participants to perform measures of selective attention, cognitive flexibility, and attentional switching. Moreover, these observations are suggestive of a sparing of psychomotor function in healthy adults who are given AD medications in a subacute administration paradigm.

Participants also completed a measure of verbal learning and memory – the RAVLT. The administration of antidepressant medication was found to have no effect on two performance dimensions of this task – i.e. mean number of items correctly recalled and the interference effect. This suggests that the consumption of escitalopram had no impact upon participants' ability to perform measures reliant on the integrity of short- and long-term memory.

As with the second experiment, the performance of participants in the n-back task was assessed during the acquisition of an fMRI scan. Analysis of the data obtained during scanning revealed a significant main effect of the level of n-back on both the mean number of correct responses and average reaction. Moreover, linear contrasts for the effect of n-back and reverse Helmert contrasts between each of the levels of the task were significant on both of these outcome measures. This indicates that the parametric increase in the level of cognitive load was evident in a linear decrease in both the mean accuracy and the mean reaction of participants, in both experimental conditions. However, the participants' medication status had no significant effect on either measure of performance. This is suggestive of a failure of subacute administration of SSRI medication in healthy adults to effect WM function.

An additional factor of interest in the analysis of n-back data was the effect of scanning session (i.e. session 1 vs. session 2) within each experimental condition. There was no significant difference between the mean accuracy of responses in the first and second scanning sessions. Moreover, although there was an apparently significant main effect of

scanning session and a significant interaction effect involving scanning session and level of n-back on participant reaction time, post-hoc analysis revealed that scanning session only had an impact on reaction time at the 0-back level of the task. This finding is similar to the results of experiment two, which further suggests a possible effect on performance of factors which are likely to change as a result of multiple scanning sessions, such as stress and arousal.

Therefore, it would appear that the subacute administration of antidepressant medication to normal healthy volunteers had no effect on the accuracy of the measure of working memory used in this study, i.e. the n-back task. Moreover, antidepressant medication had no impact on participants' reaction time at each level of n-back. Both of these findings are consistent with the normal performance of participants on the TEA, which was indicative of a sparing of executive function and psychomotor ability in the experimental sample. The findings are also in accordance with the observations of other investigations of the effect of SSRI medications on cognitive function in normal healthy adults (e.g. Hindmarch, 1988; Hindmarch & Kerr, 1994; Hindmarch, 1995; Fairweather et al., 1997; Nathan, Stough & Siteram, 2000).

- Comparison of behavioural findings: Experiment two vs. experiment three- medicated, healthy volunteers vs. depressed patients

The analysis of behavioural findings in the second study was indicative of two types of impairment of cognitive function associated with major depression. The first of these was slowing of psychomotor function, which was evident in the increased reaction time of depressed patients on the visual elevator task. The second observed deficit was a decrease in mean accuracy of patients on the n-back task. The failure to observe a similarity in the behavioural performance of the depressed patients in the second study and the healthy volunteers in the post-medication phase suggests that the impairments that were noted in experiment two are more likely due to MDD, rather than an effect of AD medication in depressed patients.

However, it is essential to note that the effect of AD medication in normal healthy volunteers is not necessarily the same as the impact of similar medications in clinically depressed patients. Indeed, there may be an interaction effect between AD medication and features of

MDD, which brings about impairments specific to the administration of AD medication to clinically depressed individuals. Therefore, prior to drawing conclusions relating to the effect of antidepressants on cognitive function in patients with major depression, based on observations of the effect of such medications in normal controls, it is important that such potential interactions are taken into account.

Of particular interest in the comparison of behavioural findings was the observation of a relative speeding up of reaction time associated with the linear increase in the level of n on the n-back task in both experiments two and three. While there was a main effect of n on reaction time in the first investigation, post-hoc analysis revealed that there was only a relative improvement in psychomotor function with the incremental increase between the 0- and 1-back levels of the task. However, in the case of the latter investigations post-hoc analysis found that each subsequent parametric modulation of task difficulty resulted in a significant decrease in participants' reaction time, thus suggesting that psychomotor ability and task difficulty may be in someway linked. Moreover, the results of experiments two and three indicate that this effect may be generalised to different and varied populations, given that the effect was noted not only in depressed patients and healthy controls but also in a sample of medicated, healthy controls.

Given the sparsity of relevant background literature relating to this type of phenomenon it is difficult to postulate potential mechanisms for the relationship between these two factors. One potential explanation is that the correlation between the level of n-back and reaction time may be modulated by increased state stress and/or arousal, such as would be expected to be induced as a result of the increased task difficulty. For example, as the level of n increases the number of items participants are required to retain in the central executive increases, in order to clear the executive for new items in higher task levels participants may experience a greater pressure or immediacy in their need to respond, hence resulting in a notable decrease in their response times. While this is one potential explanation for the observed effect, it is impossible to draw conclusions in the absence of objective data to corroborate the notion of increased stress and arousal during task performance, e.g. such as heart rate or skin conductance measures. It is also important to note that while one could argue that the effect of n-back on stress, and hence reaction time, may be the result of time

rather than difficulty, the counterbalancing of the order of presentation of n-back levels in the two scanning sessions would infer that difficulty is the critical factor here.

Functional neuroimaging results

Given the findings of previous studies of the effect of antidepressants on cognition in normal healthy volunteers, the observation of no significant effect of escitalopram on measures of cognitive function was not unexpected. However, the predicted effects of this class of medications on cerebral metabolism are less clear. Therefore, analyses of functional imaging data was designed to determine whether the subacute administration of escitalopram resulted in significant alterations in the pattern of functional activation during performance of the n-back task.

Alterations in regions of cortical activation associated with the linear increase in difficulty were determined for participants during medication-free and post-medication experimental conditions. In addition, the patterns of significant activation associated with each condition were compared in order to determine relative differences in activation associated with the administration of antidepressant medication. Given that there was no observed difference in the behavioural measures of n-back performance between medication-free and post-medication conditions, patterns of cortical activation were determined for the original block design only (i.e. rather than repeating the previous event related analysis).

In the medication-free condition the increase in the level of difficulty of the n-back task resulted in increased activation in the superior and inferior parietal lobes, in the middle and superior frontal gyri, and the cerebellum. However, as in the previous study, the pattern of decreased activation associated with the same parameter changes was evident in a more diffuse range of cortical areas, including a range of frontal and temporal regions, such as the inferior, middle, and superior frontal gyri, the pre- and postcentral gyri, the middle and superior temporal gyri, the angular gyrus, the claustrum, and the parahippocampal gyrus. Moreover, decreased activation was also noted in the right cerebellum.

The increase in task difficulty in the post-medication condition was also associated with increased activation in the frontal and parietal cortices. Regions of significantly increased activation included both inferior and superior parietal lobes and the inferior, middle, and

superior frontal gyri. Increased activation was also noted in the insula and the precuneus. Decreased activation, on the other hand, was noted in fewer regions in the post-medication condition, yet still involved a relatively diverse network of frontal (i.e. superior frontal and cingulate gyrus) and temporal (i.e. middle temporal and angular gyri) regions. In addition, decreased activation was also noted in occipital regions in the post-medication scanning condition – including the cuneus and the lingual gyrus.

Although there appears to be a difference in the number of regions involved in the performance of the task in two experimental conditions, the random effects analysis revealed no regions of statistically significantly different activation between the two experimental conditions. Thus, it may be the case that the same regions were activated in both conditions, but that in one or other of the conditions the effect may have been below the threshold for detection. Alternatively, the random effects analysis may have been too conservative to detect genuine differences in the cerebral activation of participants in the medication-free and post-medication condition. Indeed, for the purpose of the random effects analysis the data were treated as if they were between-subjects, rather than repeat measures. Thus, the actually estimated variance in the random effects analysis was likely to have been greater than expected for the current within subjects design.

In order to determine whether this latter assertion was correct, fixed effects contrasts were constructed, with the following factors of interest: level of difficulty of n-back and the relative effect of medication status. The results of this analysis revealed medication related increases in activation in a single cluster, which comprised the middle frontal gyrus and the anterior cingulate (BA24), and a relative decrease in activation in clusters in the middle occipital and superior temporal gyri, and the cerebellum.

Overall, the analysis of the functional imaging data acquired in experiment three was indicative of a similar pattern of changes in cortical activation associated with the increase in difficulty of the n-back task in both the medication-free and post-medication conditions of the investigation. However, there is tentative evidence of alterations in the cerebral metabolism of a few regions as a result of the administration of antidepressant medication to the ten healthy volunteers who participated in this study. However, these latter findings are based on observations from a fixed effects analysis, and would need to be replicated in a

suitable random effects analysis before any they can be generalised to healthy volunteers on escitalopram per se.

- Comparison of functional neuroimaging findings: Experiment two vs. experiment three - Medicated, healthy volunteers vs. depressed patients

The regions of increased and decreased activation associated with the increase in the level of difficulty of the n-back task were relatively consistent between experiments two and three. Indeed, the increased activation of both parietal and prefrontal regions was noted consistently in the analysis of the functional imaging data in both experiments. Moreover, a diffuse pattern of decreased activation was also noted in the analyses of all experimental groups, across both studies.

A major finding of the functional imaging data in experiment two was the relative increase in activation in the MOPFC/rAC in depressed patients, compared to controls. The initial random effects analysis of the functional activation of participants in experiment three revealed no regions of significantly different activation related to medication status. This implies that the abnormality in MOPFC in depressed patients was the result of factors specific to MDD, rather than antidepressant medication. While, a secondary fixed effects analysis of the functional imaging data in experiment three was indicative of medication effects on the magnitude of AC activity (see Appendix 3C), this cluster was more dorsally located than the significant cluster of interest in the second study. The spatial dissociation between these two clusters in experiments two and three is indicative of the fact that the noted MOPFC/rAC dysfunction in depressed patients is the result of some factor of depressive illness, rather than an outcome due to the impact of antidepressant medication in our patient sample. Nonetheless, it is important to note that the differential effect on cerebral metabolism may simply be due to the sampling of different experimental populations, and that at this stage it is difficult to rule out medication effects in our depressed sample.

As with the behavioural results, of primary concern is the extent to which the effects of antidepressant medications in healthy volunteers can be generalised to clinical populations. Indeed, previous studies of the metabolic effects of AD medications have found cortical differences in metabolism in treatment-responsive patients, but not in healthy volunteers

(e.g. Kalin et al., 1997; Bonne et al., 1999; Mayberg et al., 2000; Kennedy et al., 2001; Drevets et al., 2002). This implies that the effects of antidepressants on regional cerebral metabolism may depend on the interaction between medication and factors relating to symptom reversal, rather than just medication alone.

In this instance it is also important to note that the observed differences in AC activation in experiment three are inferred from the results of the fixed effects analysis of the functional neuroimaging data. Fixed effects analyses are normally associated with the impression of increased statistical power, as a result of their failure to take account of the individual variability of participants. However, the use of a repeated measures paradigm in experiment three actually removed at least one source of variation in the analysis, which should make the results of the fixed effects analysis more reliable and thus more credible. Therefore, it may be asserted that the differences observed between participants while medication-free and after medication in the fixed effects analysis may reflect genuine difference related to the administration of escitalopram. Consequently, the relative increase in activation in the AC in the post-medication condition in the fixed effects analysis in experiment three may be associated with the similar effects seen in depressed patients in other experiments

The accuracy of this assertion can partially be determined by the examination of the evidence relevant to the relative differences in the action of antidepressant medication between healthy volunteers and depressed patients. In addition, the clarification of the nature of the dysfunction noted in experiment three can be ascertained by exploring the evidence relating to the role of the anterior cingulate in cognitive function and the integrity of AC function in MDD.

The issues arising from the analysis of both the behavioural and functional imaging data from this series of investigations, and how they contribute to our understanding of the aetiology of cognitive dysfunction in major depressive disorder will be explored in the following sections of this chapter.

8.2 Discussion

Having considered the outcomes of each of the studies separately, the following subsections attempt to integrate the results of the studies that constituted this project with the findings of

previous investigations that are pertinent to the understanding of cognitive performance and cortical function in patients with major depressive disorder.

8.2.1 Working memory function in major depression

Despite the proposition that the observed deficits in cognitive function in depressed patients may be attributed to a deficit in the central executive component of human working memory (i.e. Channon et al., 1993), investigations of working memory in MDD have been inconsistent in their observations. One potential explanation for the discrepancy in the experimental outcomes of different studies is a lack of appropriate sensitivity in the measures of working memory that have been employed. Therefore, the use of a more suitable measure of working memory, which allows for manipulation of the contributory processes of WM, should enable the construction of a more accurate account of this form of executive function in depressed patients. This assertion was a central component of the current series of investigations.

It has already been noted that a primary aim of both experiments one and two was the estimation of the integrity of working memory function in major depression. More specifically, both of these investigations aimed to determine whether the use of a more sensitive measure of WM, which could be varied in order to increase the level of difficulty by manipulating the magnitude of cognitive load (i.e. the n-back task), would produce more distinct and reliable differences between depressed patients and healthy controls.

The analyses of the results in both studies were indicative of a notable impairment in working memory function in adults with MDD. The impairment of WM was observed in measures of accuracy in both experiments one and two. However, the manipulation of the level of cognitive load in the working memory task did not have a differential effect on the performance of patients. Indeed, it appeared that the deficit seen in patients on the n-back task was consistent in nature, thus, suggesting that the magnitude of cognitive load was not necessarily the primary cause of WM deficit in depressed patients, and that the deficit may be the result of another factor that contributed to performance.

It has been suggested that the profile of cognitive dysfunction in major depression can largely be attributed to the degree of psychomotor impairment experienced by depressed

patients. Therefore, it is possible that the executive dysfunction that was noted in depressed patients in experiments one and two may be attributable to the noted deficit in psychomotor ability. However, although depressed patients were noted to be significantly slowed on the n-back task compared to controls in the first experiment, in experiment two there was no observed effect of depression on reaction time measures in the n-back task, yet depressed patients were still relatively impaired on this task. Indeed, the effect size for the difference in accuracy between patients and controls was found to larger in the second study. Consequently, while psychomotor function is likely to be a contributory factor in cognitive performance in depressed patients, abnormal psychomotor ability is not sufficient to explain the differences in performance of the patients and controls on the n-back task in the experiments in this study.

Alternatively, it could be argued that motivation had played a critical role in the performance of depressed patients on the n-back task. Indeed, a consistent deficit in motivation may result in a consistent impairment in cognitive performance. Whether depressed patients experienced reduced motivation in this study can be partially determined by consideration of aspects of the data used to calculate the event-related contrasts. In order to conduct the event-related analysis of the functional imaging data acquired in the second study it was necessary to construct models of the individual responses for each participant. This was achieved by using the response data for each participant, and within each data set identifying four classes of response, i.e.: (1) correct actual response; (2) correct no response; (3) incorrect actual response; and (4) incorrect no response. If motivation were a primary factor in the relative detriment in the performance of patients, it would be reasonable to suppose that the differences in the mean number of correct items at each level of difficulty of n-back could be attributed to a failure of depressed patients to respond to individual stimulus items. This type of difference would be evident in an increased number of 'incorrect no response' items across the levels of n-back. However, when the pattern of results was examined for both patients and controls, it was noted that patients had a greater tendency to respond incorrectly, than to not respond at all. Thus, indicating that motivation to perform the n-back task was not necessarily reduced in depressed patients in these studies.

Other potential factors that may have contributed to the performance of depressed patients were also determined to have had a minimal effect on the group differences. For example, the differences in the mean estimated IQ of patients and controls was noted to contribute to the performance of both experimental groups at the 0-back level of the task, but had little impact on the observed group differences. In addition, other factors that have been noted to contribute to the cognitive performance of depressed patients in other studies, such as severity of depression and other clinical factors were found to have little effect on the extent of the performance of depressed patients on the n-back task in these studies. Therefore, it would appear that the differences between the performance of depressed patients and healthy controls on the n-back task can be reasonably attributed to a factor of working memory performance, rather than some other contributory factor, such as motor impairment, motivation, or IQ.

Although there was not a differential effect of the level of cognitive load on the degree of deficit exhibited by depressed patients on the working memory task, the dysfunction of patients on the n-back task may still be attributable to an abnormality in executive processes in major depression. However, as opposed to an impairment related to the level of cognitive load of a given measure of executive function, the dysfunction of working memory may be due to a consistent level of difficulty experienced by depressed patients on such measures. The notion of a general and consistent level of perceived difficulty on measures of executive function is supported by the observed differences in the performance of patients and controls on the TEA subtests in experiment one. In addition, although the differences between patients and controls on the TEA subtests were not statistically significant in experiment two, the mean scores of patients on the visual elevator task were relatively less than those of controls (i.e. both raw and scaled scores).

The findings of this study do not entirely rule out the likelihood of an effect of cognitive load in depressed patients, but instead suggest that the magnitude of load may have to be increased beyond the levels explored here in order to detect a differential profile of perceived difficulty in depressed patients and healthy controls. Support for this notion comes from the observed levels of performance of both depressed patients and healthy controls at the 3-back level of the variation of the n-back task used in this study. Indeed, although depressed patients were relatively impaired compared to controls at all levels of

the task, at the maximal levels of task difficulty both groups continued to perform at a greater than chance level. However, if the difficulty of the task was increased, in order to induce levels of performance that were near ceiling levels in the depressed group, then the magnitude of the difference in the performance accuracy of depressed patients and healthy controls may begin to differentially increase.

Consequently, the behavioural findings of this study are indicative of an impairment of executive function in patients with MDD, which is not attributable to other factors of depressive illness, such as psychomotor dysfunction or motivation. However, the manipulations of the working memory task used in this study were not extensive enough to allow us to determine whether this deficit is attributable to a dysfunction of central executive function or whether it can be accredited to more general task difficulty related impairment.

8.2.2 Regional abnormalities in brain metabolism in major depression

One potential way to address the issue of the aetiology of the types of executive deficits noted in the behavioural findings of these experiments is to examine the metabolic correlates of the performance of the n-back task, and to compare regions of significant difference between depressed patients and healthy controls on putative regions of activation supporting working memory function.

The comparison of the regions which exhibited significant alterations in their degree of activation in response to the linear increase in difficulty of the n-back task, revealed relatively few differences between depressed patients and controls. However, a significant difference in the magnitude of decreased response in response to an increase in cognitive load was noted in the MOPFC/rAC between patients and controls. Although, both groups experienced this decrease, the extent of decreased activity was significantly less in depressed patients. Therefore, in the data analysis this difference was noted as a relative increase in patients.

In order to determine the role of this apparent dysfunction in the observed behavioural dysfunctions that were noted in the performance of the n-back task in depressed patients, it is important to consider the potential role of this region in cognition and affect in normal healthy adults, whether MOPFC dysfunction has been noted other functional neuroimaging

studies of major depression, and the relationship of functional abnormalities of MOPFC in depression to the cognitive profile of depressed patients.

8.2.2.1 Medial orbitofrontal prefrontal cortex function and major depression

The activation of the medial orbital frontal region of prefrontal cortex has been implicated in a number of cortical functions in both normal healthy adults and clinical samples. Moreover, it has been postulated to play a role in both cognitive and affective processing. For example, studies of guessing (i.e. vs. knowing) in normal healthy adults have found a significant increase in the activation of orbitofrontal prefrontal cortex (i.e. BA11/25; Elliott, Rees & Dolan, 1999). Similarly, significant activation of this region has also been noted in investigations of response inhibition. Horn and colleagues found that in a sample of normal male participants noted significant responses in the right medial orbitofrontal cortex during performance of a 'Go/No-go' task (i.e. Horn et al., 2003).

Of particular relevance to the study of functional abnormalities associated with major depression is the role of MOPFC in the previously discussed abnormal response to negative feedback that has been noted in depressed patients (see section 1.1.3.2, pp32-33 for full details). In their investigation of the response of depressed patients to feedback, Elliott and colleagues found a highly specific focal functional abnormality in patients with unipolar depression in the MOPFC in response to feedback, compared to conditions of no feedback (Elliott et al., 1998). These investigators found that in comparison to healthy controls, activation in this region was significantly attenuated in depressed patients, in both hemispheres, in those conditions were feedback was given.

It is possible that the abnormal response of MOPFC in situations of feedback in depressed adults may be to some degree mediated by the role of this region in modulating stress and anxiety responses. In an investigation of the neuroanatomy of anxiety, it was noted that the presence of anxiety (i.e. in adults with a diagnosis of one of three anxiety disorders) was associated with activation of the right posterior medial orbital frontal cortex, in comparison to healthy control participants (i.e. Rauch et al., 1997).

This notion of the role of MOPFC in the modulation of affective responses is further supported by evidence regarding the role of the rostral and ventral sections of the AC in

affect. Indeed there is evidence to suggest that lesions of this region can result in variety of dysfunctions of affect, including apathy and emotional instability (see Bush, Luu & Posner, 2000 for a review). Moreover, the induction of sad mood in normal healthy adults has been shown to activate this region of cortex and rAC has been shown to be activated in adults with major depression (in Bush et al., 2000).

In addition to a function in affective and cognitive processing in normal and clinical populations, there is evidence to suggest that MOPFC may play a significant role in the response of unipolar depressed patients to anti-depressant medication. A series of studies by Helen Mayberg and colleagues have highlighted the role of rostral (subgenual) anterior cingulate in the treatment response profile of MDD patients (e.g. Mayberg et al., 1997; Mayberg et al., 2000). In an early study Mayberg noted that hypometabolism in rAC characterised treatment non-responders compared to healthy controls. Responders, on the other hand, were noted to be hypermetabolic in the same region. Moreover, in this study this was the only region which uniquely differentiated between responders and non-responders (Mayberg et al., 1997). These findings were supported by similar observations in a later study by the same author. In an examination of regional metabolic effects of fluoxetine in MDD non-responders were again characterised by a failure to note changes in the subgenual AC (Mayberg et al., 2000). Again, these observations are likely to be linked to the affective function of MOPFC/rAC. More specifically, it could be suggested that the hypoactivation of this region in treatment responsive patients may simply reflect the persistence of the affective symptoms of MDD.

In a recent review of imaging studies of major depression, Mayberg suggested that as opposed to the classic lesion-deficit approach to imaging of depression that we should consider observed metabolic patterns in MDD as "a combination of 'functional lesion' and an on-going process of attempted self-correction or adaptation" (Mayberg, 2003: p 196). Within this proposed framework hypermetabolism may be viewed as a compensatory activation of regions of cortex (i.e. frontal areas) in response to the chronic activation of limbic-subcortical structures, with the aim of overriding the persistent effect to such activity on affect. Conversely, Mayberg suggests that hypometabolism is the result of a failure to initiate or maintain this compensatory response in frontal cortical regions, thus resulting in

the persistence of negative affect, psychomotor dysfunction, and impaired executive function.

Having considered the potential, and varied, roles of MOPFC/rAC the important question is how this reflects upon the observed increase in activity in this region in depressed patients, compared to controls, in our second experiment. The results of the analysis of the functional imaging data from experiment two suggest that not only did depressed patients exhibit a relative increase in this area with the parametric increase in the level of n-back, but that this hyperactivation was associated with those instances where patients were performing the task incorrectly.

The primary assumption may be that the due to an increased level of state stress and arousal in depressed individuals (i.e. as measured prior to scanning) may have increased the level of activation of the noted MOPFC/rAC. However, it is important to determine how such an increased level of stress may have impacted upon the performance of depressed participants, such as would bring about the noted impairment of this group across levels of the n-back task. One potential account of this effect comes from a review of the reciprocal suppression of blood flow in affective vs. cognitive task by Drevets and Raichle (i.e.Drevets & Raichle, 1998). In their review, these authors suggest that cognitive: affective distinction that has been noted between dorsal and rostral aspects of AC, respectively (see below for further details) is often reflected in a pattern of reciprocal suppression during one type of task or the other. Based on this assumption, it could be asserted that the increased activation that was noted in the second study in MOPFC/rAC in depressed individuals may have had the effect of suppressing activation in the dorsal AC, which is a region previously noted to be involved in aspects of task difficulty in the performance of tests of WM.

The increased activation MOPFC in MDD patients in experiment two can be partially explained by the evidence from the work of Mayberg and colleagues considered above. However, while the hypermetabolism of MOPFC in depressed individuals would suggest that our patients were treatment responders and that the increased activity of this cluster is indicative of an attempt to compensate for the over activation of limbic-structures, it has already been noted that the average duration of current depressed episode in our depressed

sample was relatively long, thus suggesting that at least some of our participants would have been potentially classed as non-responders.

With respect to the role of MOPFC activation in the cognitive profile of our participants there are two key factors: MOPFC activation under conditions of guessing and MOPFC activation in situations of feedback.

As discussed above, situations of guessing may incur increased activation in the MOPFC in normal healthy controls, primarily in the RH. It is possible that in trials where depressed patients were unsure of the correct answer they would be more likely to guess the correct response. Indeed, this notion is supported by the fact the patients were more likely to make an incorrect response, rather than to not respond at all. Therefore, the increased activation of MOPFC/rAC in depressed patients, relative to controls, may have reflected those instances in which they were unsure of the correct response and were more likely to respond incorrectly. While this assertion fits well with the behavioural and functional observations, it should be noted that in experiment two the relevant cluster was on the LH, as opposed to the RH, as in Horn's study, which may have implications for the reliability of this interpretation of the data.

The variation of the n-back task that was used in this series of investigations did not include any form of explicit feedback for participants during task performance. This was done in order to minimise the effects of feedback on performance of the depressed participants. Based on previous findings, the inclusion of feedback in this paradigm may have been predicted to result in an attenuation of activation in the MOPFC in depressed individuals. Conversely, it could be suggested that the absence of feedback would result in a failure of depressed participants to reduce the level of activation in MOPFC/rAC. Although, this does not fully explain the relative increase in activation seen in depressed patients, it is likely to be a contributory factor in the observed profile of cerebral activation in experiment two.

Given the complexity of the function of MOPFC/rAC it is difficult to ascertain an unequivocal account of the differences in activation that were noted between the depressed patients and the healthy controls who participated in experiment two. However, it is likely that the contributory role of this cortical region to both cognitive and affective processing,

i.e. due to it's own functional diversity and it's reciprocal connections to regions of cortex also involved in both types of function, at least partially accounts for the role of MOPFC in the observed deficit in performance of depressed patients on measures of executive function.

8.2.3 The impact of escitalopram on measures of cognition and cerebral metabolism in healthy volunteers

The lack of a significant effect of the administration of escitalopram on any of the measures of cognitive function in experiment three was in agreement with the observations of previous investigations of the effects of SSRI medication in normal healthy volunteers. Prior studies of the effects of both the acute and subacute administration of AD medication to normal healthy adults have tended to note that SSRI medications have little or no effect on the profile cognitive function (see Chapter 1: section 1.3).

Although it could be asserted that this pattern of results may be specific to healthy volunteers, reviews of both single and multiple dose administrations of ADs indicate that the cognitive profile in medicated healthy volunteers appears to mimic the observations of cognitive function associated with the chronic administration of antidepressants in clinically depressed individuals (see Amado-Boccara et al., 1995 for a review). This implies that the cognitive dysfunctions in depressed individuals can be attributed to the presence of depressive symptoms, rather than the administration of antidepressant medication. Moreover, these findings indicate that any deficits in cognition that are associated with antidepressants should also be apparent in healthy volunteers who are given the same kinds of medication. Therefore, it would appear that the deficits noted in executive function in depressed patients in the first and second experiments are not the result of antidepressant medication, but are related to the experience of MDD.

The available evidence is suggestive of a lack of a significant association between SSRI medications and cortical metabolism in healthy volunteers. This notion was further supported by the failure to note a behavioural difference in working memory performance associated with medication status, and the results of the initial random effects analysis of functional imaging data. Support for the notion of spared cerebral function in medicated healthy volunteers come from previous findings of the specificity of changes in cortical metabolism resulting from antidepressant medication. Indeed, the available data suggests

that SSRI medications induce changes in cerebral perfusion in treatment responsive adults with MDD only.

However, the secondary fixed effects analysis of functional imaging data in experiment three indicated that medication status was associated with increased activation in the same region as was noted to be dysfunctional in the depressed patients, i.e. the anterior cingulate (BA24). Despite the reduced power of this finding, it is suggestive of an effect of antidepressant medication on metabolism in the healthy volunteers who participated in experiment three. Moreover, although one may question the reliability of this observation this region is one that has been consistently implicated in cognitive function in normal, healthy adults, and which is known to exhibit functional abnormalities in patients with MDD. Therefore, it is important to consider the potential role of such a dysfunction in previously noted cognitive deficits in depressed adults.

Anterior cingulate function has an integral role in both cognitive and affective processing in normal health adults, with its contribution to both classes of function being largely described as 'executive'. In support of the diverse nature of AC function, lesions of this area have been noted to result in a variety of symptoms, including dysfunction of attention, apathy, deficits in autonomic function, akinetic mutism, and emotional instability (Bush et al., 2000). Across both cognitive and affective domains, it has been suggested that the anterior cingulate is involved in initiation, motivation, and goal-directed behaviours (Devinsky, Morrell & Vogt, 1995).

With respect to the contributions of the AC to both cognitive and affective processing, it has been suggested that the cytoarchitecture of the AC can be subdivided into regions that are specialised for the cognitive and affective processes it is involved in (i.e. dorsal and rostral-ventral, respectively; see Bush et al., 2000 for a review). The regions of anterior cingulate which are involved in the mediation of cognitive function have been noted to have a number of reciprocal connections to other regions of cortex, including dorsolateral PFC (BA 46/9), parietal cortex (BA 7) and both premotor and supplementary motor areas (Devinsky et al., 1995). It has been suggested that the dorsal anterior cingulate cortex contributes to executive processing via these reciprocal connections using a range of functions, including response selection, competition monitoring, complex motor control, error detection, and, crucially,

working memory (e.g. Devinsky et al., 1995; Bush et al., 1999; Carter, Botvinick & Cohen, 1999).

With respect to working memory performance, the previous review of putative regions of activation in working memory tasks was indicative of the role of anterior cingulate in working memory function (see Chapter 1, section 1.2). A number of investigations have noted significant changes in the level of activation in the anterior cingulate during the performance of working memory tasks (e.g. Schumacher et al., 1996; Braver et al., 1997; Callicott et al., 1999; Jansma et al., 2000). Jansma and colleagues found a large regions of load sensitive activation in the anterior cingulate (i.e. Jansma et al., 2000). However, it has been suggested that the alteration of anterior cingulate activity is a crucial response to the level of task difficulty, rather than a load-dependent response (e.g. Barch et al., 1997).

The pattern of AC function in resting state and functional activation studies of MDD has not been consistent. While some studies have found alterations of AC function in depressed patients, including both increases (e.g. Videbech et al., 2002) and decreases (e.g. Bench et al., 1992; Bench et al., 1993; Elliott et al., 1997; Kumari et al., 2003), other investigations have failed to find any evidence of a dysfunction of AC associated with MDD (e.g. Saxena et al., 2001; Videbech et al., 2003). However, these differences may reflect inter-study variation in factors pertinent to the observation of metabolic differences between healthy controls and depressed patients. Indeed, in a review of cingulate gyrus function, Ebert & Ebmeier, (1996) found evidence of altered anterior cingulate perfusion in a range of functional imaging studies of the relationship between depressive symptoms and cerebral metabolism.

Although one study found evidence of a reduced cerebral blood flow in rostral AC (i.e. Kumari et al., 2003), given the functional distinction of the anatomical substructures of the AC this abnormality in cingulate function may instead reflect affective, rather than cognitive, processes. However, studies of cognitive dysfunction in MDD have noted significant correlations between AC activity and memory function in depressed patients (e.g. Dolan et al., 1994). Therefore, the evidence from functional neuroimaging studies of major depression appears to support the notion of a dysfunction of anterior cingulate associated with both affective and cognitive aspects of depressive symptomology.

The observations of the role of anterior cingulate activation in both normal participants and depressed patients supports the notion that the observed dysfunction in the anterior cingulate in the patients in experiment two was a contributory factor to the observed deficit on the behavioural measures of the n-back task in this experimental group. The dorsal location of the cluster of significantly increased AC activation in the depressed patients (i.e. BA 24) suggests that the abnormal activity of the AC was associated with the pattern of executive dysfunction seen in depressed patients, rather than being related to the affective abnormalities noted in the patients. Given the varied role of the dorsal anterior cingulate, it is difficult to ascertain which aspect(s) of working memory function are likely to be impaired by this type of abnormality.

While there is considerable evidence to suggest that the anterior cingulate is involved in executive processes, determining the specific role of AC in measures of WM is a relatively difficult process. However, there is evidence to suggest that the function of this cortical region may be restricted to aspects of task difficulty associated with the performance of parametric measures of working memory, rather than cognitive load.

8.3 Further research recommendations

Further investigation of the performance of individuals with MDD on the n-back measure of working memory, during functional neuroimaging, is recommended for a number of reasons. Firstly, it is suggested that the extension of the maximal levels of difficulty of the n-back task would allow for the estimation of whether depressed patients experience of differential decrease in performance as the level of cognitive-load approaches ceiling levels of performance, compared to controls. This type of manipulation should allow for the further clarification of whether depression associated deficits in working memory are simply the result of the effect of factors such as a generalised task difficulty, state stress, or sensitivity to performance feedback, or whether memory load does indeed play a significant role in depressed patients' ability to undertake such measures.

Moreover, this type of manipulation of the n-back task might alter the metabolic effects noted in the second experiment. Indeed, it is possible that increasing task difficulty may enable a clearer definition in the role of the MOPFC in modulating the performance of depressed patients on this type of measure, by allowing a more detailed exploration of the

corresponding behavioural data. Similarly, a differential decrease in performance as a result of increased load on the central executive may be reflected in functional abnormalities in putative regions of central executive function, such as the dorsolateral prefrontal cortex.

As previously noted, the depressed samples that participated in the first and second experiments were a relatively specialised group of patients. They were comparatively young cohort, with respect to other studies of this type, and they tended to exhibit symptoms of chronic depressive illness. Therefore, the repetition of this paradigm in larger and more varied groups of depressed participants is recommended. It is likely that this would help to address the issue of whether the lack of significant differences on specific aspects of behavioural performance are the result of the relatively small and specialised experimental groups who participated in functional neuroimaging in this study. In addition, such replication of the experimental paradigm would also allow for the determination of whether, or not, the observations in these studies are specific to young, chronically ill depressed patients, or whether the type of deficit that were noted (i.e. both behavioural and functional) are characteristic of a wider population of depressed individuals.

A significant limitation, which was noted post-hoc, was the failure to include physiological measures of stress and arousal during scanning. Although this would have been useful in general in extrapolating the relationship between various variables of interest, it would have been of particular use in exploring the association between psychomotor function and task difficulty. Therefore, in future studies of this sort it may be practical to include some sort of measure of physiological arousal, such as breathing or heart rate or skin conductance, during functional imaging.

The final recommendation for further research is the repetition of the paradigm used in experiment three. There are relatively few studies of the effects of AD medication on cerebral metabolism in healthy volunteers, and the results from this study are not entirely unequivocal. Therefore, further investigation of this issue is warranted in order to ascertain an accurate profile of cerebral metabolism associated with medicated status. This will not only aid in the clarification of such effects in healthy volunteers but will also assist in

determining which aspects of functional abnormality in MDD can be attributed to depressive illness and which are the result of a patient's medication status.

8.4 Conclusions

In conclusion, the results of the series of investigations that comprised this study were indicative of a dysfunction of executive processes in adults with major depressive disorder, relative to matched healthy controls. This dysfunction included measures of selective attention, cognitive flexibility, and attentional switching, in addition to a main deficit in working memory function (i.e. as measured using the n-back task).

The degree of disparity in the performance of depressed patients and healthy controls could not be attributed to group differences in IQ, nor was it the result of impaired psychomotor function or reduced motivation in depressed individuals. The origin of the working memory deficit noted in depressed patients appeared to be the result of a dysfunction of an aspect of the performance of measures of working memory pertaining to task difficulty, rather than manipulations of the magnitude of load on the central executive component of the working memory system.

This latter assertion was partially supported by the observation of abnormal activity in thee MOPFC/rAC in depressed patients, associated with the linear increase in the level of difficulty in the n-back task, i.e. patients were found to experience a relative increase in the level of functional activation in this region. In addition, consideration of the event related responses in cortical activation suggest that the increased activation in this region was related to both affective and cognitive responses to task difficulty in those instances in which patients performed the task incorrectly (i.e. stress/arousal and guessing, respectively).

In the final experiment altered activity in the anterior cingulate was observed in a fixed effects analysis of functional imaging data from a group of healthy volunteers who had been given a short-course of an SSRI medication. While this observation did not have a direct impact upon the observations of this study it does have implications for the interpretation of the observation of AC dysfunction in previous neuroimaging studies of MDD. For example it could be suggested that the altered activity in the AC of depressed patients could

potentially be attributed to the medication status of individuals with MDD, rather than being symptomatic of depressive illness.

In comparison to previous investigations of working memory function in MDD, this study has been successful in demonstrating a dysfunction of human working memory in depressed adults. The results of the functional neuroimaging data are indicative of a dysfunction in the medial orbital prefrontal cortex/rostral (subgenual) anterior cingulate, which is likely to have contributed to the observed behavioural differences in depressed patients and healthy controls on the measures of executive function that were used in this study, via mediation of both affective and cognitive function.

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Appendix One: Literature review summary tables

Appendix 1A: Summary of cognitive deficits in depression

Notes: 1. Unless otherwise indicate, 'Depressed' denotes individuals with unipolar, major depressive disorder and 'Controls' denotes matched, healthy controls. Additional descriptions of participant groups are noted where necessary. 2. The citations for each of the assessments employed in each study are as appeared in the original text, and refer directly to the version of the task used in the given investigation. 3. Identification of specific cognitive functions relating to assessments where possible are those identified by the investigators. Where the specific function under investigation has not been outlined in the paper in question the function outlined in the table approximates to cognitive functions identified in other investigations utilising the same (or similar) assessments 4. For those studies where depressed individuals were compared to patients with other psychiatric conditions (e.g. schizophrenia) only those data relating to significant effects in the depressed group are outlined. 5. Data are presented relating to any exploratory factors included in each study, i.e. factors that may affect the severity of deficit observed in individuals with major depressive disorder.

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Austin et al. (1992)	Depressed (40) (i.e. 20 endogenous & 20 neurotic) vs. Controls (20)	1. Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964, Lezak, 1983) 2. Digit symbol substitution test and block design (DSST) (WAIS-R; Weschler, 1981) 3. Digit span forwards (DGF) and digit span backwards (DGB) (WMS-R; Weschler, 1987) 4. Trail making A & B (Army Individual Test Battery, 1944) 5. F·A·S verbal fluency (Borkowski, et al., 1967) 6. National Adult Reading Test (NART; Nelson & O'Connell, 1978)	Novel learning (1) Immediate memory (recall) (1 & 3) Short-term memory (STM) (recall and recognition) (1) Psychomotor speed (2, 4, & 5) Concentration (4) Attention (4)	Both endogenous and neurotic groups impaired on AVLT – both recall and recognition. Endogenous group more impaired than neurotic on DSST and trail A & B	Impairment was significantly correlated with severity of depression (i.e. HRSD & Newcastle scales), after co-varying for age. No association between clinical variables (e.g. family history of affective disorder, personal history of attempter suicide etc.) and cognitive function. No effect of consumption of medication on cognitive function.

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	*Significant effects* [4]	Factors of Interest [5]
Austin et al. (1999)	Depressed (77) (i.e. 39 melancholic & 38 non-melancholic) vs. Controls (28)	1. DGF & DGB (WMS-R) 2. Reaction time A (i.e. simple) & reaction time B (i.e. choice) (Hubbert, 1987) 3. Trails A & B 4. Stroop task (Golden, 1978) 5. F·A·S verbal fluency (Borkowski, et al., 1967) 6. Wisconsin Card Sorting Test – Abbreviated (WCST-64; Heaton, 1981) 7. Similarities (WAIS-R) 8. Rey AVLT 9. Visual reproduction (WMS-R) 10. DSST (WAIS-R) 11. NART (Nelson, 1982)	Attention (1) Immediate recall (1) Psychomotor speed (2 & 5) Information processing speed (2) Set-shifting ability (2, 3, 6, & 9) Visuomotor speed (3 & 9) Selective attention (4 & 9) Ability to conceptualise (7) Immediate memory (recall) (8) Short-term memory (recall & recognition) (8)	Depressed sample most impaired on mnemonic tasks, simple reaction time, and Trails B. Melancholic patients additionally impaired on WCST (perseverative response) and DSST. Cognitive performance of non-melancholic patients largely unimpaired.	Neuropsychological test scores inversely correlated with depression severity (i.e. HRSD) and psychomotor disturbance. No effect of medication status on cognitive function. Also little effect of psychosis and age on level of impairment.
Bartolic et al. (1999)	Euphoric (30) vs. dysphoric (30) (i.e. mood induced, healthy controls)	1. Controlled Oral Word Association Test (COWAT; Benton & Hamster, 1983) 2. The Ruff Figural Fluency Test (RFFT); Ruff, 1988)	Verbal fluency (1) Figural fluency (2)	Euphoria associated with better verbal than figural fluency. Dysphoria associated with better figural than verbal fluency. Implications for the role of affect in the function of the frontal lobes.	N/A
Bazin et al. (1994)	Depressed (23) (i.e. in-patients) vs. Controls (37)	1. Cued recall 2. Word-stem completion	Implicit memory (1) Explicit memory (2)	Depressed patients impaired on cued-recall but not word-stem completion. Effect disappeared upon recovery.	N/A

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Beats, Sahakian, & Levy (1996)	Elderly depressed (24) vs. Controls (15)	1. WAIS-R short form – i.e. vocabulary, comprehension, DSST, block design, and object assembly. 2. NART (Nelson, 1982) 3. Kendrick Cognitive Tests for the Elderly (KOLT and KDCT; Kendrick, 1985) (i.e. for dementia screening) 4. F·A·S verbal fluency (Milner, 1964) 5. CANTAB: a. Working memory and planning battery – spatial span (Milner, 1971), spatial working memory (Petrides and Milner, 1982), spatial planning (Tower of London (TOL); Shallice, 1982)) b. Attentional battery – set-shifting task (Downes et al., 1989), reaction time (simple and choice), visual search task (Treisman & Gelade, 1982), c. Visuospatial memory battery – pattern recognition, spatial recognition, delayed match-to-sample (DMTS; Mishkin, 1982), paired-associate learning (Owens et al., 1985)	Psychomotor speed (4, 5(b) – i.e. simple reaction time) Short-term memory (5(a) – spatial span) Working memory (5(a) – spatial working memory) Planning (5(a) – TOL) Set-shifting (5(b)) Information processing speed (5(b) – choice reaction time) Visual selective attention (5(b) – visual search) Visuospatial memory (5(c))	Depressed patients impaired on all tests compared to controls and themselves at recovery. Thus depression in the elderly associated with a significant degree of deficits on tests sensitive to frontostriatal dysfunction – some of which are specific to depression, and some that do not remit upon recovery.	Response latency of performance measures in patients correlated significantly with number of depressive episodes experienced. Age of onset inversely correlated with response latency measures.
Brand, Jolles, & Gispen-de Wied (1992)	Depressed (24) (i.e. DSM-III-R classification: 13 dysthymic, 7 major depressed, 2 atypical, & 2 bipolar) vs. Controls (26)	Word-learning task (adapted from RAVLT; (Lezak, 1983; Mayes 1986) – 1, 3 & 5 trial variations	Immediate memory (recall) Short-term memory (recall and recognition)	Patients impaired on recall on 1 & 5 trial learning task. On 3 trial learning task not impaired except for immediate recall. Patients significantly slower than controls on recognition task- but recognised similar number of words. Data suggest impaired retrieval and encoding of information – especially when processing demands are high.	N/A
Brébion, Smith, & Widlocher (1997)	Depressed (26) vs. Controls (26)	Word recognition task	Response bias Discrimination	Mean discrimination index was lower in depressed patients than controls. No difference in the index of response bias between groups.	Severity of depression (i.e. MADRS) was related to discrimination. Psychomotor retardation was related to response bias.

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Brown, Bench, & Dolan (1994)	'Unimpaired' depressed (UD) (10) vs. 'Impaired' * (19) vs. Controls (C)(20) (unimpaired/impaired distinction determined by assessment on the CAMCOG index of the CAMDEX (Roth et al. 1988)) * - 10 'borderline impaired' (BD), 9 'impaired' (ID)	1.CAMCOG 2.Mini-Mental State Examination (MMSE; Folstein et al., 1975) 3.WAIS-R (Weschler, 1986) – vocabulary, similarities, comprehension, arithmetic, and digit-span 4.Schonell Graded Word Reading Test (Schonell, 1942;Nelson and McKenna, 1975) 5.Weschler Logical Memory (LM) and Word-Pair Associate Learning Test (PALT; Weschler, 1945) 6.RAVLT (Taylor, 1959) 7.Brown-Peterson (BP) test (Brown, 1958; Peterson & Peterson, 1959) 8.Verbal fluency –'free', 'category', and 'letter' 9.Token Test (Spreen & Benton, 1969) 10.Weigl Test (Weigl, 1941)	Language function Memory – recall and recognition Attention Behavioural regulation	<u>UD</u> Impaired on a range of measures. Those most sensitive to depression included recall memory (especially after delay), aspects of recognition memory, short-term memory (where rehearsal is prevented), verbal fluency, and language comprehension. **UD vs. BD vs. ID** Majority of cognitive tests revealed a gradient of function i.e. UD>BD>ID	Absence of any significant relationship between cognitive function and any index of depression relating to severity, symptomology, or treatment.
Channon & Green (1999)	Depressed (23) vs. Control (23) (12 individuals in each group were randomly allocated to 'strategy-aid' condition. Remaining participants allocated to 'no strategy aid' condition)	1. Memory for categorised words task (Channon, et al., 1989) 2. Sentence completion task (adapted from the Hayling test (Burgess & Shallice, 1996)) 3. Multiple scheduling task (adapted from the six elements test (Shallice & Burgess, 1991))	1. Recognition 2. Response suppression 3. Executive function	Depressed participants performed worse than controls on all three measures, and used appropriate response strategies less often. Provision of strategy hints increased the use of performance strategy in tasks (1) and (2), but did not significantly improve performance in either group.	No significant correlations between measures of severity (i.e. HRSD and BDI) and any of the performance measures.
Channon (1996)	Dysphoric (28) vs. Control (28)	WCST (Heaton, 1981)	Set-shifting	Dysphoric individuals took more trials to complete the task and more errors (i.e. both perseverative and non-perseverative). Data support the notion of impaired central executive function in dysphoric individuals.	

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Channon, Baker and Robertson (1993)	Depressed (24) vs. Controls (21)	1. Phonological similarity effect (Wilding and Mohindra, 1980) 2. Word length effect (adapted from Baddeley et al., 1984) 3. DGF (Weschler, 1981) 4. Forward block sequence (Weschler, 1981) 5. DGB (Weschler, 1981) 6. Backward block sequence (Weschler, 1981) 7. Paced Auditory Serial Addition Test (PASAT; following Gotham et al., 1988) 8. Trail-making test (Reitan, 1958) 9. Letter cancellation test (Diller et al., 1974)	Working memory (1.-3. Phonological loop, 4. Visuospatial sketchpad 5.- 9. Central executive)	Some evidence of impairment of tests of central executive function, with relative sparing of the phonological loop and visuospatial sketchpad.	No significant correlations between self-report measures (i.e. BDI and Leyton Obsessional Inventory (Snowdon, 1980), and the State Trait Anxiety Inventory (Spielberger et al., 1970), past history of depression, past history of dysthymia, or score on HRSD, to medication status (i.e. medicated vs. unmedicated) with scores on the backward digit span and PASAT.
Cohen et al. (1982)	Depressed (11) (i.e. 3 euthymic, 3 moderate, and 3 severe: 2 bipolar patients) vs. Controls (5)	1. Motor task – force exerted (in kg) in squeezing a dynamometer, and duration of half-maximal response 2. Memory task – recollection of trigrams	Changes in motor and memory response associated with mood shift	No difference between depressed and controls in left- or right-hand peak force. Duration of half-maximal response significantly less in depressed group. Severely depressed patients showed a rapid decline in memory performance with time of recall compared to other subgroups.	Deficits in motor and cognitive performance seemed to be proportionate to severity of depression (i.e. HRSD & BDI)
Cohen et al. (1999)	Schizophrenics (26 inpatient & 27 outpatient) vs. Depressed (25) vs. Controls (31)	1. AX version of the context processing test (AX-CPT); Servan-Schrieber, Cohen, & Steingard, 1997) 2. Stroop task (MacLeod, 1991) 3. Lexical disambiguation task 4. Digit span 5. Word span recall	Context-processing (1) Selective attention (2) Inhibition (2) Language processing (3) Short-term memory (4 & 5)	Depressed patients did not differ from controls on the AX-CPT, or on the accuracy measure of the Stroop. Compared to controls, depressed patients showed no tendency for facilitation in the long ISI condition of the Stroop (i.e. for reaction time). Depressed patients did not differ from controls in the number of context-biased responses in task 3. No significant differences between depressed patients and controls for either measure of STM,	N/A

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Denny & Hunt (1992)	Depressed (16) vs. Controls (16)	1. Free recall task 2. Word-stem completion task Both tasks using affectively valenced words	Explicit memory (1) Implicit memory (2)	In the explicit memory task controls recalled more words than depressed patients. Moreover, depressed patients were more likely to recall negatively valenced words than positively valenced words. The opposite pattern was observed in the controls. No effect of group or word valence in the implicit memory task.	N//A
Elderkin-Thompson et al. (2003)	Minor depressed (28) vs. Major depressed (26) vs. healthy elderly (38)	1. Modified Card Sort Test (MCST; Nelson, 1976) 2. Trail making A & B (Lezak, 1995) 3. Block design (Weschler, 1981) 4. California Verbal Learning Test (CVLT; Delis, et al., 1987) 5. Boston Naming Test (BNT; Kaplan, et al, 1983) 6. Continuous Visual Memory Test (CVMT; Trahan & Larrabee, 1988) 7. Semantic fluency (Laine, 1988) 8. DGF & DGB (Weschler, 1987) 9. MMSE	Verbal learning and recall (4 & 7) Maintenance of set (1) Executive function (2 (B), 3, & 5) Nonverbal recognition memory (6) Working memory (8)	Controls performed better than major depressed patients on tests of verbal recall and maintenance of set. Major also performed worse than minor depressed individuals on these measures. Controls performed better than minor depressed individuals on tests of executive functioning. Working memory was borderline for separating controls and major depressed	Partial correlations controlling for age and education indicated that performance declined with increase severity of depression (i.e. HRSD).
Elliot & Greene (1992)	Depressed (10) vs. Controls (10)	1. Cued recall 2. Free recall 3. Word-stem completion 4. Homophone spelling	Explicit memory (1 & 2) Implicit memory (3 & 4)	Depressed patients were significantly impaired on both of the explicit tasks and both of the implicit tasks compared to controls.	N/A

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Elliot et al. (1996)	Depressed (28) vs. Controls (26)	1. NART 2. CANTAB test battery – (a) Pattern and spatial recognition, (b) Simultaneous and delayed match-to-sample (SMTS & DMTS), (c) spatial span, (d) spatial working memory, (e) TOL, (f) New TOL, (g) attentional set-shifting task (i.e. ID/ED paradigm – ID: intra-dimensional, ED: extra-dimensional). 3. F·A·S verbal fluency (Benton, 1968)	Recognition memory (2(a)) Visuospatial memory (2(a), 2(b), 2(c)) Spatial working memory (2(d)) Set-shifting (2(e)) Planning (2(f) & 2(g))	Patients were significantly impaired on F·A·S, pattern and spatial recognition (accuracy and reaction time), SMTS, DMTS (accuracy and reaction time)*, spatial span, spatial working memory (i.e. more errors and less use of strategy) TOL & new TOL (i.e. global deficit in performance accuracy and slower on two-and three-move problems, but faster on four- and five-move problems) No significant groups differences in movement times on TOL and on attentional set-shifting. * - covarying for MTS latency removed the significant group effect on DMTS latency	Significant effect of failure on subsequence performance in patients – i.e. motivational deficit. Significant correlation between clinical rating scores (i.e. HRSD, Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), & Clinical Interview for Depression (CID) (Paykel, 1985)) and neuropsychological deficits – especially mnemonic deficits.
Fossati et al. (1999)	Depressed (20) vs. Schizophrenic (14) vs. Controls (20)	1. P·R·V verbal fluency (Benton, 1968; Cardebat, et al., 1990) 2. DGF & DGB (WAIS-R) (Weschler, 1981) 3. Cognitive estimate (Shallice & Evans, 1978) 4. WCST (modified version, Nelson, 1976) 5. Delis Test (card sorting test) (adapted from Delis et al., 1992) 6. Grober & Buschke's memory task ('free and cued selective reminding' adapted from Grober, et al., 1988) (i.e. verbal learning task)	Spontaneous cognitive flexibility (1 & 5) Reactive cognitive flexibility (a) Set shifting (4) (b) Set maintenance (1 & 4) Initiation (1 & 5) Selection (1 & 3) Working memory (1,2,3,4, & 5) Episodic memory (6)	Depressed patients exhibited executive but not mnemonic i.e. task 6) deficits. Deficits in several 'higher-level' functions combined to produce executive impairments in depressed patients – including complex integration for concept formation, spontaneous cognitive flexibility, and initiation ability	No correlation between clinical ratings of symptom severity (i.e. MADRS) and cognitive performance. Mean duration of depressive episode was correlated with semantic fluency.

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Goldberg, et al. (1999)	Depressed (29) vs. Schizophrenic (57) vs. Bipolar depressed (16)	1. WAIS-R short form (Silverstein, 1985) 2. Wide Range Achievement Test – Revised (WRAT-R) reading test (Jastak & Wilkinson, 1984)) (i.e. a measure of premorbid intellectual function) 3. WMS-Form II (a) Visual reproduction (b) Paired associate learning (c) Logical memory 4. WCST (Axelrod, et al., 1992) 5. The Category Test (LaLonde, 1985) 6.Line orientation (Benton, et al., 1978) 7. Facial recognition (Benton, et al., 1978)	Visuomotor speed (3(a)) Selective attention (3(a), 4) Recall (3(a), (b), and (c)) Set-shifting (4) Concept formation (5) Cognitive flexibility (5) Problem solving (5)	Schizophrenic patients more impaired than affective patients on tests of psychomotor speed, attention, memory, and problem solving.	In depressed patients, symptom severity (i.e. Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) accounted for more than 28% of variance in cognitive performance.
Golinkoff & Sweeney (1989)	Depressed (18) vs. Personality disorder (18) vs. Controls (18)	1. Frequency of occurrence 2. Paired associate learning	Automatic processing (1) Effortful processing (2)	No impairment of automatic processing. In effortful tasks depressed patients had a tendency to recall and recognise fewer words than controls. Results suggest that the poorer performance of depressed patients reflect basic memory impairments rather than a general inability to allocate cognitive effort to more demanding tasks.	There was no significant correlation between severity of depression (i.e. HRSD) and recall or recognition scores.

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Grant, Thase, & Sweeney (2001)	Depressed (123) vs. Controls (36)	1. Halstead-Reitan Trail Making Test (Part A) 2. Digit span test 3. CPT (Cornblatt, et al., 1989) 4. The Hopkins Verbal Learning Test (Brandt, 1991) 5. Visual reproduction (WMS-R; Weschler, 1987) 6. Halstead-Reitan categories test 7. COWAT (F-A-S) 8. WCST (Heaton, 1981) 9. Trail Making Test (Part B) 10. CANTAB 11. The Stockings of Cambridge Task (based on TOL; Shallice 1982) 12. Spatial working memory task 13. ID/ED Attentional Set-shifting task 14. Spatial recognition memory task 15. SMTS & DMTS 16. Pattern recognition memory task 17. Paired associated learning 18. Spatial span test	Psychomotor speed (1) Verbal attention (2) Sustained attention (3) Verbal memory (4) Immediate and delayed visual memory (5) Executive function (6 – 10) Concept formation (6 & 8) Verbal fluency (7) Maintenance (8) Set-shifting (8, 13) Cognitive flexibility (9) Planning (11) Working memory (12) Visuospatial memory (14 – 18)	No significant differences between depressed patients and healthy subjects on any measure of attention, psychomotor functioning, or mnemonic measures. Depressed patients were impaired on the WCST on several parameters, including number of categories completed, perseverative responses, perseverative error, and failures to maintain set. No deficits were seen in other test of executive functioning.	No significant correlation between severity of depression (i.e. BDI & HRSD) and measures of executive functioning, memory, attention, or psychomotor performance. Modest relationships between clinician rated severity of depression and performance on some tests from the CANTAB. Differences in performance on DMTS, ID/ED & WCST are persistence of depressive symptoms Significant age-corrected correlations for ages of onset of first episode, psychomotor speed, and executive functioning – i.e. later onset associated with greater decline in performance.
Grossman et al. (1993)	Depressed (44) vs. Controls (44)	Kaufman Adolescent and Adult Intelligence Test (KAIT; Kaufman & Kaufman, 1993)`	Tertiary memory Planning ability Secondary memory – delayed and immediate recall	Depressed patients did not differ significantly from controls on KAIT variables, but did differ significantly on the delayed vs. immediate recall of verbal information.	N/A

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Ilsley, Moffoot, & O'Carroll (1995)	Depressed (15) vs. Controls (15)	1. MMSE 2. DGF & DGB 3. Rivermead behavioural memory test (RBMT) 4. Oral verbal fluency task (a) Letter prompt (m) (b) Semantic category (animal) 5. Silly sentences test (Colllins & Quillian, 1969) 6. Word stem completion 7. DSST	Short-term memory (2) Episodic memory (3 & 6) Semantic memory (4 & 5) Implicit memory (6) Psychomotor speed (7)	Patients were unimpaired on short-term memory, recognition, semantic memory and implicit memory. However, compared to controls patients showed significant deficits in psychomotor sped and free recall (i.e. both immediate and delayed) – i.e. suggestive of spared encoding and impaired search and retrieval processes. No evidence of a hedonic bias in recall of positive and negatively valenced items.	No correlation between severity of depression and level of memory impairment. Presence of psychotic symptoms did not effect the cognitive profile observed in patients.
Kessing (1998)	Euthymic depressed (118) vs. Euthymic bipolar (28) vs. Controls (58)	1. CAMCOG 2. The Mattis Dementia Rating Scale (MDRS; Mattis, 1976) 3. The Gottfries-Brane-Steen (GBS) Dementia Rating Scale (Gottfries, et al., 1988) 4. MMSE 5. Global Deterioration Scale (GDS; Gottfries, et al., 1982)	Language (1 & 2) Attention (1 & 2) Abstract thinking (1 & 2) Verbal and non-verbal short- and long-term memory (1 & 2) Calculation (1 & 2) Perception (1 & 2) Praxis (1 & 2)	Patients with only one episode did not differ from controls on any measure. Patients with more than one episode were significantly impaired on all measures vs. controls.	BDI score correlated significantly with MMSE, GBS, and GDS. No. of episodes significantly associated with CAMCOG and MDRS measures.
Landrø, Stiles, Sletvord,(2001)	Depressed (22) vs. Controls (30)	1. Finger tapping (i.e. two tasks from the Automated Psychological Test (APT; Levander & Elithorn, 1987) 2. Choice reaction time (from APT) 3. Trail making A & B 4. DSST 5. PASAT – A & B (i.e. 4.0 & 2.0 sec, respectively) 6. DGF 7. Randt Memory Test (Randt, Brown, & Osbourne, 1980) 8. Kimura Recurring Recognition Figures Test (Kimura, 1963) 9. COWAT 10. WAIS-R Block Design 11. WAIS-R similarities	Motor function (1) Selective attention (2) Mental flexibility (3 (i.e. difference between A & B) Visuomotor tracking (4) Working memory (5) Short-term memory (6) Long-term memory – verbal and non-verbal (7 & 8) Verbal fluency (9) Visuospatial function (10)	Significant differences between groups in selective attention, working memory, verbal long-term memory, and verbal fluency – i.e. patients worse. Selective deficit in depressed patients on selective attention and working memory. Short-term memory least impaired in depressed patients. On the choice reaction time task, depressed patients were significantly slower to respond with left-hand than controls.	N/A

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MacQueen et al. (2002)	Depressed (40) vs. Controls (40)	1. NART (Nelson, 1982) 2. Cognitive Failures Questionnaire	Recollection memory	Patients had impaired recollection memory but no impairment in habit memory compared to controls.	Impairment was not predicted by indices of current mood (i.e. HRSD & SCID) but was predicted by self-assessment of mood (i.e. BDI-II) and past number of depressions. No evidence of effect of medication on performance
Merriam et al. (1999)	Depressed (79) (i.e. unmedicated for min. 28 days) vs. Schizophrenic (47) vs. Controls (61)	WCST	Set-shifting	Depressed patients made more errors (i.e. both perseverative & non-perseverative), took longer to reach the first category, completed fewer categories overall, had fewer conceptual-level responses and lower learning-to-learn scores than controls.	HRSD scores moderately correlated with the number of categories achieved, number of perseverative errors, number of perseverative responses and the percentage of conceptual level responses.
Miller et al. (1991)	Depressed (28) vs. Controls (28)	Luria-Nebraska Neuropsychological Battery (LNNB; Golden, et al., 1985)	Memory Intellectual processes Psychomotor activity Auditory attention Sustained attention Visual memory Verbal encoding Verbal memory	No significant differences between patients and controls – except on a single measure of attention.	No significant correlations between symptomology (i.e. measured using HRSD) and cognitive performance
Moffoot et al., (1994)	Melancholic depressed (20) (i.e. patients with clear diurnal variation) vs. Controls (20)	1. DGF & DGB(following Randt & Brown, 1983) 2. DSST 3. RAVLT 4. CANTAB – (a). RT (b). SMTS & DMTS 5. Dynamometer hand squeeze task	Attention Concentration Psychomotor speed (2 & 4(a)) Working memory (1) Verbal learning and memory (3) Visuospatial memory (4(b)) Motor performance (5)	Morning pattern of neuropsychological impairment: attention, concentration, working memory, episodic memory, RT & speed of SMTS, and motor performance. Evening pattern of impairment: psychomotor slowing, and visuospatial memory	Morning cortisol correlated with diurnal improvement in neuropsychological functioning.

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Moritz et al. (2002)	Depressed (25) vs. Schizophrenic (25) vs. Obsessive-Compulsive (25) vs. Controls (70)	1. WCST (Loong, 1990) 2. Stroop Task (Moritz, Mass & Junk, 1998) 3. Trail Making A & B (Reitan, 1992) 4. DGF & DBG 5. (Creative) verbal fluency (Schoppe, 1975)	Set-shifting (1) Selective attention (2) Inhibition (2) Concentration (3) Psychomotor speed (3) Short-term memory (4) Working memory (4) Verbal fluency (5)	Depressed patients were impaired on all measures compared to controls.	Core clinical ratings were not significantly correlated with task performance (i.e. HRSD). Data from the OCD patients indicated no significant effect of anti-depressants on performance.
Murphy et al. (1999)	Manic depressed (18) vs. Depressed (28) vs. Controls-A* (18) & Controls-B* (22) * - group A: manic matched, group B: depressed matched	1. NART (Nelson, 1982) 2. MMSE (Folstein, et al., 1975) 3. Pattern and spatial recognition memory 4. SMTS & DMTS 5. TOL 6. Affective shifting task – i.e. Go/No-go	Spatial recognition memory (3) Visuospatial memory (4) Planning (5) Working memory (5) Inhibitory control (6)	(Note: Re: Behavioural data for depressed patients – only data for task 6 presented) Depressed patients were impaired in their ability to shift the focus of attention, and exhibited bias for negative stimuli.	No significant correlations between measures of severity (i.e. HRSD, MADRS, & CID) and performance measures.
Murphy et al. (2001)	Manic depressed (18) vs. Depressed (22) vs. Controls (26)	1. NART (Nelson, 1982) 2. MMSE (Folstein, et al., 1975) 3. Decision making task (Rogers, et al., 1999a)	Decision making	Depressed patients were impaired on this task, compared to controls, i.e. slower deliberation times, failures to accumulate as many points, and suboptimal betting strategies.	Severity of depression (i.e. HRSD) was not significantly correlated with the quality of decision-making.
Murphy et al. (2003)	Depressed (27) vs. Controls (23)	1. Probability Reversal task (Swainson, et al., 2000) 2. Spatial working memory (CANTAB) (Robbins, et al., 1994, 1998) – i.e. feedback and no-feedback variations	Visual discrimination (1) Working memory (2)	Depressed patients were impaired in their ability to maintain response set when receiving negative feedback. Their ability to acquire and reverse the necessary visual discrimination was impaired. On the spatial working memory task, depressed patients made significantly more between-search errors than controls, but were still able to use negative feedback to facilitate performance.	No significant main effect of medication on performance and no significant relationship between clinical variables and neuropsychological performance.

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Palmer et al. (1996)	Older depressed* (36) (i.e. 22 predominantly vegetative symptoms, 14 predominantly psychological symptoms) vs. Controls (40) * - all depressed participants were > 45 years.	1. WAIS-R (Weschler, 1981) 2. WMS-R (Weschler, 1987) (a) Logical memory (b) Visual reproductions 3. Rey-Osterrieth Complex Figure (ROCF; Lezak, 1995) 4. Warrington Recognition Memory Test (RMT; Warrington, 1984) 5. BNT (Kaplan, et al., 1987) 6. COWAT (Lezak, 1995) 7. Stroop (Goodglass & Kaplan, 1979) 8. Auditory Consonant Trigrams Test (ACT; Stuss, et al., 1982) 9. WCST (Heaton et al., 1993)	Short-term recall (2(a)) Set-shifting (2(b) & 9) Visuomotor speed (2(b)) Selective attention (2(b) & 7) Visuospatial memory (3) Recognition (4) Executive function (5) Verbal fluency (6) Inhibition (7) Verbal memory (8)	Vegetative vs. controls: patients impaired on full scale and performance IQ measures, immediate recall in visual reproductions task, delay and retention conditions of the ROCF, recognition of faces, and on the WCST (i.e. on category, perseverative responses, and perseverative errors measures). Psychological not impaired on any measures compared to controls. Vegetative vs. psychological depressed: Vegetative patients impaired on digit span, digit symbol, and WCST (i.e. on perseverative responses and perseverative errors measures) tasks.	N/A

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Porter et al. (2003)	Medication free* depressed (44) vs. Controls (44) (* medication free for at least 6 weeks prior to testing)	1.DSST (Weschler, 1981) 2.RAVLT (Rey, 1964) 3.Paired associates learning (CANTAB) 4.Pattern Recognition (CANTAB) 5.Spatial recognition (CANTAB) 6.Simulatneous/delayed matching to sample (CANTAB) 7.FAS (Benton & Hasher, 1976) 8.'Exclude letter' fluency test (ELFT) (Bryan et al. 1997) 9.Vigil continuous performance test (Cegalis & Bowlin, 1991) 10. Spatial working memory (CANTAB) 11.TOL (CANTAB)	Neurocognitive function (1.Psychomotor performance, 2.Verbal learning and memory, 3.-6.Visuospatial learning and memory, 7.-11.Sustained attention and executive function)	Evidence of significant neurocognitive impairment in young adult, outpatients, with unipolar depression. Impairment across a range of cognitive domains – including attention/executive function, and visuospatial learning and memory. Deficits almost exclusively on measures of accuracy.	Severity of depression significantly negatively correlated with number of indices of learning and memory (i.e. RAVLT – long-term recall, long-term recognition, pattern recognition – percentage correct, delayed matching to sample, and paired associated learning – total trials. In patients cortisol/DHEA ratio was significantly, negatively correlated with performance on the DSST and positively with TOL initial thinking time. If exclude melancholic patients, FAS and delayed matching to sample trials no longer reaching statistical significance. Exclusion of patients meeting Newcastle-defined endogenous depression differences on FAS and RAVLT List B no longer reached significance.
Purcell et al. (1997)	Depressed (20) vs. Controls (20)	CANTAB: 1. 'Executive' tasks (a) Spatial span; (b) Spatial working memory; (c) TOL; (d) ID/ED 2. Visual memory tasks (a) DMTS; (b) Spatial recognition; (c) Pattern recognition	Short-term memory capacity (1(a)) Working memory (1(b), 1(c)) Planning (1(c)) Attentional set-shifting (1(d)) Visuospatial memory (2(a)-(c))	Patients were not impaired (vs. controls) on measures of STM capacity, spatial WM, planning ability, cognitive speed, DMTS, or recognition memory. Patients did show impairments on subsequent movement latencies on TOL, and on attentional set-shifting.	Medication (i.e. taking medication vs. no medication) had no effect on significant impairments. No significant correlations with age of onset, length of illness, severity (i.e. HRSD), age, IQ (NART) and education with impaired performance.

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Ravnkilde, et al., (2002)	Depressed (40) vs. Controls (49)	1. Danish Adult Reading Test (DART) (Nelson & McConnell, 1978) 2. WAIS – vocabulary, information, DGF & DGB, (Weschler, 1955) 3. Subtracting serial sevens (Smith, 1967) 4. Stroop (Stroop, 1935) 5. WAIS-R – DSST (Weschler, 1981) 6. Trail making A & B (Reitan, 1955) 7. Verbal fluency (Borkowski, Bento, & Spreen, 1967) 8. Token Test (Spellacy & Spreen, 1969) 9. Brown-Peterson Test (Peterson, 1966) 10. WMS-R – visual reproduction (Weschler, 1987) 11. Test/Logical memory test (Weschler, 1945) 12. Luria Verbal Learning Test (Christensen, 1975) 13. WCST (Heaton, 1981)	Verbal intelligence (1 & 2 (not DGF & DGB)) Attention (2 (DGF & DGB), 3, & 4) Visuomotor speed (5 & 6) Language (7 & 8) Memory (2 (DGF & DGB), 9, 10, 11 & 12) Executive function (13)	Patients performed significantly worse than controls on measures of verbal intelligence (not DART), attention, verbal fluency, short-term memory (i.e. on Brown-Peterson test – although difference was only significant at longest delay intervals, immediate recall on test/logical memory test, and the visual reproduction test). Regarding executive function, the only difference between patients and controls to almost reach significance was failure to maintain set (i.e. patients scored, on average, greater on this measure). Results could not be explained simply in terms of group differences in psychomotor speed (i.e. patients were significantly slower than controls over a range of measures). Indeed, the only significant difference that appeared to be altered by co-varying for psychomotor speed was performance on verbal fluency for words beginning with S.	Stroop, DSST, trail making, and visual reproduction all significantly correlated with severity (i.e. HRSD). There appeared to be no significant differences on neuropsychological measures between those patients receiving anti-depressant medication and those not. Similarly, duration of consumption of medication did not seem to effect these measures.

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Robertson & Taylor (1985)	Depressed (12, i.e. 6 unipolar and 6 'reactive') vs. Bipolar (16) vs. Controls (41) (Note: all participants were imprisoned at the time of assessment, the majority awaiting trial)	1. WAIS-R (short-form) 2. Verbal fluency (a) free association (b) category (c) F & S 3. Visual retention: (a) simple verbal (b) mixed function (c) 'faces' 4. Visual recognition: (a) alphabet (b) embedded letter (c) broken letter (d) broken figure 5. Schonell Graded Word Reading Test	Verbal fluency Visual memory	Unipolar vs. controls: Impaired on verbal fluency (i.e. category and F & S), performance intelligence (i.e. picture completion, picture arrangement, and block design), visual retention (i.e. simple, mixed, and faces), and visual recognition (i.e. embedded letter, broken letter, and broken figure). Reactive vs. controls: Impaired on verbal fluency (all tasks), verbal intelligence (i.e. digit span), performance intelligence (i.e. picture arrangement), and visual retention (i.e. faces)	N/A
Roy-Byrne et al. (1986)	Depressed (10) vs. Controls (10)	1. Simple information processing 2. Sustained effort and information processing	Automatic processing (1) Effortful processing (2)	Depressed individuals were significantly impaired on the effortful task compared to controls but not on the automatic task.	Suggested that poorer free recall of the entire depressed group is likely to be a medication effect.
Shah et al. (1999)	2 studies: 1. Depressed (20) vs. Acute schizophrenia (20) vs. Chronic schizophrenia (40) vs. Controls (40) 2. Depressed vs. Controls	SMTS & DMTS (CANTAB)	Visual memory	Depressed patients were impaired on both SMTS and DMTS compared to controls.	Depressed patients did not show an abnormal response to negative feedback. Moreover, response to negative feedback was not effected by diurnal variation.
Sweeney, Kmiec, & Kupfer (2000	Depressed (58) vs. Bipolar (35) vs. Controls (51)	1. TOL 2. Spatial WM 3. ID/ED 4. Spatial recognition 5. SMTS & DMTS 6. Pattern recognition 7. Paired-associate learning 8. Spatial span 9. Big circle/little circle 10. Five stage reaction time	Planning (1) Working memory (2) Attentional set-shifting (3) Visuospatial memory (4, 5, 6, & 7) Short-term memory (8) Psychomotor speed (9 & 10)	No group differences in tasks 9 & 10 – i.e. cognitive differences due to differences in processing rather than differences in motor speed. Significant deficits in depressed restricted to episodic memory.	Severity of depression (i.e. HRSD) and severity of psychosis (i.e. Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) was significantly correlated with several aspects of cognitive performance. No significant effect of difference classes of medication. Age was associated with test performance

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Tham, et al., (1997)	Euthymic patients (26) (i.e. Manic (9) vs. Depressed (10) vs. Both manic and depressed (7)) vs. Controls (not specified) Note: patient classifications based on the type of episode that lead to their hospitalisation	1. Synonym, reasoning, and block-test (SRB) battery (Dureman, Saldë, & Batteriet, 1971) 2. Schulze 10-word test (Claeson, et al., 1971) 3. Memory for designs test (Graham & Kendall, 1960) 4. Halstead-Reitan Neuropsychology Battery (Bolls, 1981) – (a) trail-making test, (b) rhythm test, (c) finger tapping	Verbal understanding (1 – synonyms test) Visual-constructive skill (1-block design test) Verbal memory (2) Non-verbal memory (3) Visuospatial scanning and flexibility (4(a)) Non-verbal auditory perception, attention, and sustained concentration (4(b)) Motor speed (4(c))	Overall performance of euthymic patients was lower than controls. This difference was independent of the type of episode that led to hospitalisation. The only significant difference between the three patient sub-groups was on the trail-making B test – i.e. significant decline in T-scores of patients admitted for both manic and depressed episodes compared to those admitted only for episodes of depression. Patients admitted for mania only were significantly impaired on synonym and trail-making B compared with depressed only.	Number of hospitalisation episodes was significantly correlated with reasoning, general intelligence, and trail-making A & B – i.e. those patients with higher level of impairment had a greater number of hospitalisations. Only trail-making A was significantly (positively) correlated with length of illness. All other correlations for effects of age, gender, length of illness, and number of hospitalisations on cognitive function were non-significant.
Thomas, Goudeman, & Rousseaux (1999)	Depressed (10) vs. Controls (10) (Note: Patients were assessed both during period of illness and on recovery)	1. Single task – simple bimodal RT 2. Single task – choice bimodal RT 3. Dual task – simple bimodal RT 4. Dual task – choice bimodal RT	Effortful processing Automatic processing	Depressed patient improved from single to dual tasks (i.e. compared to controls and recovered who both worsened). Depressed patients showed significant impairment (i.e. both time and accuracy) on tasks that required decision-making. Suggested that deficits in attention seen in depression cannot be explained by processing resources alone.	N/A

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Trichard, et al., (1995)	Depressed (23) vs. Controls (15) (Note: Depressed sample included both unipolar and bipolar patients, but authors don't note relative numbers of each)	1. Stroop 2. Verbal fluency (F·A·S & M·P·D) 3. WAIS-R – vocabulary subtest	Selective attention (1) Inhibition (1) Verbal fluency (2)	At inclusion patients were impaired on both tasks compared with normal controls.	Time course changes – i.e. only verbal fluency normalised with successful treatment of depression. Suggest that selective deficit may persist beyond a clear clinical improvement. No significant correlation between severity (i.e. MADRS) or depressive retardation (i.e. Salpètriére Retardation Rating Scale (SRRS; Widlöcher & Ghozlan, 1989)) and psychological performance in depressives. Improvement in verbal fluency correlated with severity (i.e. MADRS).
Tsourtos, Thompson and Stough, (2002)	Depressed (19) vs. Controls (20)	Inspection time	Speed of information processing	Speed of information processing impaired in young, unmedicated, unipolar depressed patients.	No significant correlation between inspection time and level of depression (i.e. as measured using the Zung Depression Scale (Zung, 1965)). Significant negative correlation between the length of depression from first depressive episode (i.e. $p<0.05$), and a trend towards a negative correlation between inspection time and duration of current episode (i.e. $p = 0.06$)
Watkins and Brown (2002)	Depressed (14) vs. Controls (14)	1. Rumination or distraction induction task. 2. Random number generation task.	Executive function (2)	Rumination in depressed patients occupies central executive resources.	N/A

Author(s) (Date)	Participants: Type (N) [1]	Cognitive and Neuropsychological Assessment(s) [2]	Cognitive Function(s) of Interest [3]	Significant effects [4]	Factors of Interest [5]
Weingartner et al. (1981)	3 studies: 1 & 2. Depressed (10) vs. Controls (10) 3. Affective disorder (10; i.e. Depressed (4), Bipolar (Type I) (1), & Bipolar (Type II) (5)) vs. Controls (10)	1. Levels of processing learning task 2. Categorisation and recall of words	Encoding	Impairment in recall of information was most evident in patients in those processing conditions that required the use of more elaborate processing strategies. If depressed patients are provided with organisation and structure then learning-memory deficits are not apparent.	N/A
Wolfe et al. (1987)	Depressed (20) vs. Bipolar (12) vs. Huntington's (10) vs. Controls (20)	1. RAVLT 2. F·A·S	Verbal recall and recognition (1) Verbal fluency (2)	Depressed patients were impaired with respect to both recall and recognition, compared to controls. However, depressed patients were not impaired on tests of verbal fluency.	N/A

Appendix 1B: Summary of reviews of neuropsychological and cognitive function in depression

Note: Details are presented of a selection of review articles (i.e. meta-analytical, systematic, or selective in nature) which have summarised the evidence of deficits in specific domains of cognition in individuals with a unipolar depressive illness. The above selection includes reviews that have examined the data not only comparing patients with MDD with control participants but also with other psychiatric groups. Moreover, some of the reviews presented include details of studies involving complimentary methodologies (e.g. neuroimaging evidence). However, the data presented here are only those relative to the cognitive function of individuals with major depression.

Author(s) (date)	Method	Cognitive function(s) of interest	Conclusion(s)	Factor(s) of interest
Austin, Mitchell, & Goodwin (2001)	Selective computerised review – cognitive deficits in depression and their brain correlates	1. Episodic memory and learning 2. Executive function	Evidence of a number of dysfunction of both visual and verbal explicit memory with relative sparing of implicit memory. Despite early conflicts in reports, evidence of executive dysfunction across studies, which may be specific to set-shifting tasks.	Many studies suggest that reported deficits in major depression may be independent of age, severity, depressive subtype, task difficulty, motivation, and response bias. Some deficits appear to persist beyond clinical recovery.
Burt, Niederehe, & Zembar (1995)	Meta-analysis – i.e. of studies examining recall and recognition in depressed and non-depressed samples	Mnemonic function – recall and recognition	Significant impairment of both recall and recognition in depressed patients. Although, the authors note that only an association is determined by the investigation, rather than a cause, causal direction, or underlying mechanism. Results indicated that impairments of memory were characteristic of some, but not all, psychiatric disorders. Thus the possibility that impairments are associated with generalised aspects of psychopathology, rather than syndrome specific factors.	Direction of effect varied as a function of the type of memory being assessed (i.e. recall vs. recognition) or the type of study (i.e. one vs. two levels). For both recall and recognition, significant age effects indicated a greater association of impairment in younger, relative to older, patients. Moreover, memory performance was more strongly associated with depression in inpatients, compared to outpatients. Recall impairment more associated with depression in mixed vs. unipolar patients. Recognition appeared to be more associated with depression in unipolar vs. mixed patients. In one analysis, medication status was significant on recall Z scores, but not recognition. Greater depression effects on memory for positive, vs. negative and neutral, stimuli. Retention interval also had a significant effect – i.e. depression more associated with impairment in delayed, vs. immediate, recognition. The converse was true for recall. In one level recall studies, depression was more associated with visual than verbal stimuli. The opposite was true of two level recall studies. In recognition studies, one level studies showed greater association of depression in verbal, rather than visual, tasks.

Author(s) (date)	Method	Cognitive function(s) of interest	Conclusion(s)	Factor(s) of interest
Christensen, et al. (1997)	Meta-analysis – i.e. examination of performance of depressed and Alzheimer-type dementia (DAT) patients on standard and experimental clinical tests of cognitive function.	1. Intelligence 2. Verbal function 3. Perception – (a) visual and (b) auditory 4. Memory – (a) registration, (b) verbal long-term, (c) non-verbal long-term, (d) mixed, and (e) remote. 5, Conceptual ability 6. Executive function 7. Motor performance 8. Constructional ability 9. Orientation 10. Attention and tracking 11. Mental status	Significant effect sizes for depressed patients, compared to controls, on tests of intelligence, verbal function, auditory perception, memory (i.e. except mixed memory), conceptual ability, executive functioning, motor performance, constructional ability, attention and tracking, and mental status.	Patient characteristics: Older depressed patients showed greater impairments than younger depressed patients. Data suggest that given similar levels of depression, older depressed patients would still perform worse than younger patients. Inpatient status was consistently related to effect size. Endogenous depressed individuals were not more impaired than non-endogenous depressives. ECT use, and severity were also associated with severity of impairment. Task characteristics: Relative to controls, depressed patients performed proportionately worse on tests of speed and vigilance. Depressed individuals recalled more on tests with depressed content, rather than neutral or pleasant. Compared to controls, depressed patients did no better on memory tasks where the stimuli were categorised, vs. those were they were not. The same was true of visual vs. verbal tasks, and of recall vs. recognition tasks. Moreover, there was no evidence to support the proposition that the deficits seen in depression are more severe in the non-dominant hemisphere. However, performance subtests on the WAIS were more susceptible to the effects of depression than verbal tests.
Crews & Harrison (1995)	Review of studies examining the neuropsychology of depression – an it's relation to cognitive theory and therapy of depression	1. Executive function 2. Psychomotor function 3. Abstraction ability 4. Visuospatial processing 5. Constructional ability 6. Mnemonic function	Depressed patients appear to be impaired on tests of executive function (including sustained attention, motivation, and concentration), psychomotor function, abstract, visuospatial processing, constructional ability, and mnemonic function (i.e. both short- and long-term visual and verbal memory).	Performance on tests of psychomotor function is associated with severity of depression (especially in those tasks requiring sustained effort). Visuospatial and visuomotor tasks are consistently impaired irrespective of depressive subtype (e.g. reactive vs. endogenous) Overall, while the degree of deficit observed between different subtypes of patients do differ the pattern of impairment appears to be rather consistent. Similarly, severity of depression appears to only effect the degree rather than type of deficit.

Author(s) (date)	Method	Cognitive function(s) of interest	Conclusion(s)	Factor(s) of interest
Elliot (1998)	Review of the nature of neuropsychological profile in depression, the interaction between cognitive and clinical features, and the neuroimaging evidence relating to neuropsychology and neuropathology.	1.Mnemonic function 2.Executive function 3.Effortful vs. automatic processing 4.Mood congruent biases in information processing	Patients show deficits in both memory (i.e. both visual and verbal, short- and long-term) and executive function - although deficits in the latter may be more prominent in depression. While there is evidence of impairment on effortful but not automatic processing in depression, there is also contradictory evidence – therefore, need to clarify whether cognitive effort in a useful concept in explaining the pattern of neuropsychological impairment observed in depression. There is evidence to suggest that the performance of depressed patients is facilitated by the use of unpleasant stimuli (i.e. vs. pleasant or neutral stimuli). This appears to hold true for both explicit and implicit (e.g. priming) studies.	Motivation: Lack of motivation may be one clinical factor that plays a causal role in neuropsychological deficits associated with depression – but would not explain the relative sparing of certain cognitive functions seen in some studies. Thus, it is suggested that it may be the more specific issue of response to performance feedback that is the key issue (i.e. abnormal response to negative feedback in depressed individuals). Severity of depression: Inconsistencies in the reporting of the relationship between the severity of depression and cognitive performance. State vs. trait factors in depression: Balance of evidence suggests that there is a notable improvement in cognitive performance on recovery from depression. However, there is evidence to suggest that both trait and state factors contribute to the cognitive profile of depressed individuals. Hospitalisation: Inpatients perform worse than outpatients on measures on neuropsychological function. Medication: Recent evidence seems to suggest that while traditional tricyclic medication can disrupt certain aspects of cognition, more modern anti-depressants have a less noticeable effect (i.e. in both patients and controls). Age: Depression is more reliably related to cognitive impairment in elderly depressed patients than those under the age of 40 – however, this is not necessarily a straight interaction effect. There is evidence to suggest that while depression in those under 40 is more reliably associated with executive dysfunction, those over 50 show impairment that extends to memory function, and those over 70 show the additional impairment of cognitive slowing.
Hartlage, et al. (1993)	Review of studies concerned with relative performance of individuals with depression on tests of effortful and automatic processing.	1. Automatic processing 2. Effortful processing.	Depression interferes with effortful processing. Depression only minimally interferes with automatic processing.	Degree of interference on effortful tasks is determined by the degree of effortfulness of the task, the severity of depression, and the valence of the stimulus material used.

Author(s) (date)	Method	Cognitive function(s) of interest	Conclusion(s)	Factor(s) of interest
Mialet, Pope, and Yurgelun (1996)	Review of literature examining attention in depression.	1. Global attentional impairment Specific cognitive processes, i.e.: 2. Information processing 3. Automatic vs. effortful processing 4. Attentional resources 5. Selective attention	Consensus of most studies is that depressed individuals exhibit decrease cognitive efficiency on tests of attention – i.e. both impaired performance and speed. This decrease in efficiency occurs at both early and late stages of information processing. Depressed patients will exhibit a non-specific impairment of selective attention on tasks requiring speed. Memory studies of depression show that impairment is related to the overall processing requirements than to a precise memory stage, and suggest impoverishment of both input and output of information processing. However, the pattern of deficit is non-specific – i.e. similar pattern seen in other psychiatric groups.	N/A
Roediger & McDermott (1992)	Review of four studies examining implicit memory in depression	Implicit memory	Depression does not affect the amount of priming on several implicit memory tests under conditions that demonstrate marked effect on explicit memory. The mood-congruity effect also largely disappears on perceptual implicit tasks	N/A
Sobin & Sackheim (1997)	Review of studies of psychomotor function in depression	1. Speech 2. Motor response time (also considered gross motor activity and body movement)	Speech: Speech pause time and pause time at speech initiation are greater in depressed than controls. Whereas, fundamental frequency change rate, fundamental frequency variability, and rate of articulation are all decreased in depression. Motor response time: Decision time and motor response time are both increase in depression, as is the central processing component of decision time. Simple reaction time is increased in psychotic, but not non-psychotic, depression.	Course of illness, diurnal variation, medication status, sex, and age are all associated with agitation and retardation.

Author(s) (date)	Method	Cognitive function(s) of interest	Conclusion(s)	Factor(s) of interest
Tavares, Drevet, & Sahakian (2003)	Review of cognition in depression (and mania)	1. Motor function and early information processing 2. Memory 3. Executive function 4. Response to negative feedback	Studies suggest psychomotor slowing in MDD, as well as impairment in the early stages of information processing (i.e. as measured using inspection time). Evidence is also suggestive of memory dysfunction in verbal, spatial, and emotional tasks. Patients with MDD have also shown deficits on tasks of planning, decision-making, and response inhibition. Furthermore, depressed individuals exhibit an abnormal response to negative feedback.	N/A
Veiel (1997)	Met-analysis of all appropriate studies published between 1975 and 1997 examining the neuropsychology of depression.	1.Attention and concentration 2.Verbal fluency 3.Scanning and visuo-motor tracking 4.Visuospatial functions 5.Verbal learning (acquisition and retention/retrieval) 6.Non-verbal learning (acquisition and retention/retrieval) 7.Mental flexibility and control 8.Composite indicators of brain damage 9.Choice RT	No substantial differences between patients and controls in simple attention functions as measured by immediate memory span. Depressed patients showed greater variability than controls in their scores on tests of verbal fluency, scanning & visuo-motor tracking, and visuospatial functions. The proportion of patients scoring in the defective range on each of these measures was approx. 11, 18.2 and 15%, respectively. On verbal and non-verbal learning acquisition and verbal retention there was also an increase in variability of scores in MDD (% defective = 14.5, 15.5, and 15.1%). However, there was no difference between MDD and controls on the retention of non-verbal info. There was also a considerable and consistent impairment on measures of mental flexibility and control, and on the indicators of brain damage in MDD. On both these measures there was also a reasonably large dispersion of scores. There was also evidence of significant impairment of MDD patients on choice RT measures – i.e. not due to deficit in perceptual processes or stored execution of motor responses but deficient response processing.	N/A

Author(s) (date)	Method	Cognitive function(s) of interest	Conclusion(s)	Factor(s) of interest
Zakzanis, Leach, & Kaplan (1998)	Meta-analysis of studies between 1980-1997 examining neuropsychological function in depression (i.e. 22 studies meeting research criteria)	1.Episodic memory 2.Declaritive memory 3.Response initiation and persistence 4.Attention 5.Semantic memory 6.Primary memory 7.Working memory 8.Motor speed 9.Visual-perceptual conceptualisation	All those studies that were examined compared MDD patients with normal controls. Tests of episodic memory, declarative memory, response initiation and persistence and attention all showed above median effect sizes. Minimal effect sizes were noted in tests of semantic memory, primary memory, working memory, motor speed and visual-perceptual conceptualisation. There is evidence that depression has selective effects on the encoding processes in episodic memory. Moreover, there is evidence of impairment in depression of effortful or attention-demanding tasks. However, none of the effect sizes noted were large enough to allow for the complete discrimination of patients from controls.	N/A

Appendix 1C: Summary of resting state imaging studies of depression

Notes: Unless otherwise noted all studies examined individuals with MDD (i.e. 'Depressed') in comparison to matched, healthy controls (i.e. 'Controls'). For those studies where additional psychiatric groups were included, only those results pertinent to MDD are noted. 1: These three studies constitute a series of analysis on a single patient group at different time points; 2: These studies are all publications are all derived from data obtained by the Danish PET/depression project.

Author(s) (date)	Subjects: Type (N)	Method	Significant observations	Factors of interest
Austin, et al., (1992)	Depressed (40) vs. Controls (20)	SPECT with ^{99m}Tc-exametazime	Depressed group should reduced uptake in the majority of cortical and sub-cortical regions, most pronounced in temporal and inferior frontal, and parietal areas.	Strong positive association between uptake and scores on the Newcastle scale, especially in the cingulate areas and frontal cortex. Negative association between HRSD scores and anterior trace uptake.
Bench, et al., (1992) [1]	Depressed (33: 10 with severe cognitive impairment) vs. Controls (23)	PET with ^{15}Oxygen	In the depressed group rCBF was decreased in the left AC and left DLPFC. There was also a strong tendency towards decreased blood flow in right DLPFC and the left angular gyrus, and increase in the left posterior cingulate gyrus. In the cognitively impaired group there were also significant decreases in rCBF in the left medial frontal gyrus and increase rCBF in the cerebellar vermis.	No significant differences between medicated and unmedicated patients in those regions previously identified as significant.
Bench, et al., (1993) [1]	Depressed (40) vs. Controls (23)	PET with ^{15}Oxygen – i.e. examining correlation between rCBF and three factors with loadings for: (1) anxiety, (2) psychomotor retardation and depression, and (3) cognitive performance.	Despite normal global blood flow, depressed patients showed reduced rCBF in the left AC, left DLFPC, and the left angular gyrus, compared to controls. Strong trend towards a sig. Increase in the left posterior cingulate cortex (BA 23, 30). Data suggest that symptomatic specificity may be attributed to regional functional deficits in MDD. Factor 1 showed a significant positive correlation with rCBF in posterior cingulate cortex and the inferior parietal lobule bilaterally. Factor 2 correlated negatively with rCBF in the left DLPFC and left angular gyrus. Factor 3 correlated positively with rCBF in the left medial prefrontal cortex.	There was no significant difference between medicated and unmedicated patients with respect to global or regional blood flow. However, there was a trend towards a relatively decreased flow in the medicated group in the right inferior frontal lobe (BA 47).

Author(s) (date)	Subjects: Type (N)	Method	Significant observations	Factors of interest
Bench, Frackowiak, & Dolan (1995) [1]	Depressed (25)	PET with ^{15}Oxygen – i.e. longitudinal study of rCBF in patients while depressed and during clinical remission	Remission was associated with a significant increase in rCBF in left DLPFC, and medial prefrontal cortex, including AC. Increases in rCBF in the angular gyrus were not seen when the comparison of depressed and recovered scans were matched for medication. Thus the data support the notion of a recovery of blood flow in those regions that are functionally impaired when depressed – i.e. abnormalities are state related.	N/A
Brody et al (2001	Depressed (39)	PET with ^{18}FDG – i.e. changes in rCBF before and after treatment	Associations in rCBF were determined with 4 HRSD factors – i.e. anxiety (ANX), psychomotor retardation (PR), cognitive disturbance (COGN), and sleep disturbance: tension (TENS) and fatigue (FATIG). Improvement in ANX, PR, TENS & FATIG was associated with decreased ventral FL metabolism. Improved ANX and TENS also associated with decreasing ventral AC and anterior insula activity. Improved PR associated with increasing dorsal AC activity. COGN improvement was associated with increasing DLPFC activity.	
Delvenne, et al., (1990)	Depressed (38: 30 unipolar, 8 bipolar) vs. Controls (16)	SPECT with ^{133}Xenon	No significant differences between patients and controls in rCBF. However, there was a significant lateralisation of blood flow in endogenous (i.e. vs. non-endogenous) patients – i.e. blood flow was significantly lower in the LH. The same trend was observed in endogenous.	Age, sex, and HRSD score were not related to rCBF (i.e. left, right, total, or outer rim)
Dolan, et al., (1992)	Cognitively impaired depressed (10: 1 bipolar) vs. unimpaired (10: 1 bipolar)	PET with ^{15}Oxygen	Results indicated a profile of rCBF abnormalities in the cognitively impaired group that consisted of decreases in the left anterior medial prefrontal cortex and increases in the cerebellar vermis. These changes are additional to those seen in depression alone i.e. compared to controls (N=23), patients showed decrease rCBF in left and right DLPFC (BA 46), left AC gyrus (BA 32), and the right insula.	No evident significant effect of medication status, illness duration, or years of education on rCBF.
Dolan, et al., (1993)	Depressed (40) vs. Schizophrenic (30)	PET with ^{15}Oxygen – i.e. relationship between psychomotor retardation and rCBF	Independent of diagnosis, patients with psychomotor retardation (i.e. as determined by poverty of speech) exhibited significantly lower rCBF in the left DLPFC (BA 46).	N/A

Author(s) (date)	Subjects: Type (N)	Method	Significant observations	Factors of interest
Dolan, et al., (1994)	Depressed (29) vs. Controls (16) (see Bench, et al., 1994 for full details of participants and methodology)	PET with ^{15}Oxygen – i.e. correlation between resting state rCBF and principal components identified from neuropsychological data, resulting in two factors, with loadings on (1) memory and (2) attention.	Significant correlations between rCBF and patients loadings on the first principal factor (memory) in the cingulate cortex (BA 32 & 24), the medial frontal gyrus (BA 10 & 9), with areas that encompassed the retrosplenial cortex, the precuneus, and the posterior cingulate cortex (BA 31, 30, & 23), the inferior parietal lobule (extending to the angular gyrus) and the middle and superior temporal gyri. With regards to the second factor, significant correlations were evident in superior and medial frontal gyri, inferior post-central gyrus, inferior parietal lobule, and the posterior aspect of the middle temporal gyrus confluent with the left angular gyrus.	N/A
Drevets, et al., (1997)	Depressed (17) vs. Bipolar (21) vs. Controls (21)	PET	Depressed patients showed a decrease in activity in the PFC ventral to the genu of the corpus collosum. This decrement was at least partly explained by a corresponding reduction in cortical volume in this region.	N/A
Drevets, et al., (2002)	Depressed (21: 12 familial pure depressive disorder (FPDD), 9 depression spectrum disorder) vs. Bipolar (15: 7 bipolar-depressed, 8 bipolar-manic) vs. Controls (12)	PET with ^{18}FDG – i.e. examining glucose metabolism in the amygdala	Left amygdala metabolism was increase in both the FPDD and bipolar-depressed groups, compared to controls.	Left amygdala metabolism was positively correlated with stressed plasma cortisol levels in the unipolar depressed patients.
Hickie et al., (1999)	Depressed (25: unipolar and bipolar, ratio not specified)	SPECT with ^{99m}Tc-HMPAO- i.e. correlation between resting state rCBF and psychomotor performance	Changes in rCBF in the left neo-striatum were inversely correlated with RT – i.e. patients with greatest psychomotor retardation showed least rCBF increase during performance of choice reaction time.	Effects on rCBF during performance of the RT tasks were independent of age.
Lubar, Congebo, & Askew (2003)	Depressed (15) vs. Controls (15)	LORETA	Between groups comparison of spectral power revealed a decrease in activity in the right middle temporal gyrus (BA 21, involving BA 20,22) in the depressed group.	N/A
Mathew, et al., (1980)	Depressed (13) vs. Controls (13)	^{133}Xenon inhalation	Depressed patients exhibited lower gray matter flow values in the left hemisphere compared to controls. A similar trend was observed for the right hemisphere, but failed to reach significance.	rCBF values of the depressed group were significantly, inversely, correlated with HRSD score – i.e. for both left and right hemisphere.

Author(s) (date)	Subjects: Type (N)	Method	Significant observations	Factors of interest
Ravnkilde, et al., (2003) [2]	Depressed (40) vs. Controls (49)	PET with ^{15}Oxygen – i.e. correlation between resting rCBF and a number of principal components extracted from scores on a neuropsychological battery	The cognitive deficits seen in depressed patients were not associated with the rCBF of the anatomical structures that were affected in this group (i.e. hippocampus, DLPFC, orbitofrontal cortex, and AC cortex). Analysis of the association between cognitive function and functional activation in each of the experimental groups revealed significant differences between patients and controls in the following regions of interest: right orbitofrontal cortex, left temporal cortex, left anterior cingulate, left and right hippocampus, left caudate nucleus, left posterior cingulate, and right prefrontal cortex.	N/A
Sackheim, et al., (1990)	Depressed (41: 25 unipolar, 16 bipolar) vs. Controls (40)	^{133}Xenon inhalation	Depressed group showed a decrease in global cortical blood flow compared to controls. Moreover, depressed patients exhibited abnormality in topographic distribution of blood flow – i.e. due to flow reduction in selective frontal, central, superior temporal, and anterior parietal regions. This patter may reflect dysfunction in the parallel distributed cortical network involving frontal and temporoparietal polymodal association areas.	The extent of topographic abnormality was associated with both age and severity of depression (i.e. HRSD), but not with medication status or depressive subtype.
Saxena, et al., (2001)	Depressed (27) vs. OCD (27) vs. OCD + MDD (17) vs. Controls (17)	PET with ^{18}FDG	Left hippocampal metabolism was significantly lower in MDD alone and OCD + MDD patients than in OCD alone or controls. Moreover, thalamic metabolism was significantly elevated in OCD and MDD alone. In addition, patients with OCD + MDD had significantly lower metabolism in the thalamus, caudate and hippocampus than OCD alone. Other selected regions of interest, which showed no significant main effect of participant group, included (bilaterally) the caudate, DLPFC, dorsal and ventral AC, OFC, putamen, and VLPFC.	Hippocampal metabolism was negatively correlated with severity of depression (i.e. HRSD). HRSD score was also significantly negatively correlated with normalised metabolism in the left and right amygdala

Author(s) (date)	Subjects: Type (N)	Method	*Significant observations*	*Factors of interest*
Skaf, et al., (2002)	Depressed (21: 9 with psychotic features, 12 without) vs. Controls (12)	SPECT with ^{99m}Tc-ECD (ethyl-cisteinate-dimer)	Decreased rCBF in the subgenual portion of the left AC cortex (BA 25), and insular, lateral temporal and parietal cortices, and increased rCBF in the right cerebellum and left occipital cortex in psychotic depressed compared to controls. Compared to non-psychotic depressed patients, those with psychotic features showed decreased rCBF in AC and inferior frontal cortex, and increased rCBF in the right cerebellum. After co-varying for HRSD score the finding of reduced rCBF in the subgenual AC in psychotic vs. non-psychotic depressed patients remained significant.	There was a significant negative correlation between HRSD score and rCBF in right dorsal AC, and between psychomotor retardation scores and rCBF in right rostral AC. Moreover, there was a trend towards a significant positive correlation between psychomotor retardation sub-scores in the psychotic depressed group and rCBF in the right posterior cingulate cortex. No significant correlation involving the subgenual AC or insula in either depressed group.
Tutus, et al., (1998)	Depressed (10) vs. Bipolar (7) vs. Controls (9)	SPECT with ^{99m}Tc-HMPAO (hexamethylpropylene)	During depressed episode, unipolar depressed patients showed a relative increase in rCBF in the left frontal cortex compared to both controls and bipolar patients. These differences tended to disappear on remission. Remitted, depressed patients also exhibited a higher perfusion index (PI) in the right temporal region than controls.	Positive correlation between anxiety scores (i.e. CAS: Snaith, et al., 1982) and right frontal PI values. HRSD was not significantly correlated with rCBF. While length of illness was not significantly related to rCBF, length of current episode was significantly positively correlated with PI in left and right parietal regions.

Author(s) (date)	Subjects: Type (N)	Method	Significant observations	Factors of interest
Videbech, et al., (2001) [2]	Depressed (42) vs. Controls (47)	PET with ^{15}Oxygen	After controlling for effects of age, gender, years of education, and degree of lateralisation, patients exhibited a significant increase in blood flow to the right hippocampus and the left cerebellum compared to controls. There was also a trend towards increased flow in the left lateral occipito-temporal gyrus in patients compared to controls.	There was a significant increase in the proportion of blood flow in the parietal and temporal lobes in female compared to male participants. With increasing age there was an increase in the proportion of blood flow to the brain stem, thalamus, left occipital lobe white matter, left medial occipito-temporal gyrus and right hippocampal formation and a concurrent decrease in flow to the caudate nucleus, left insula, inferior frontal gyrus (bilaterally), right superior occipital and left superior temporal gyri. Years of education, degree of lateralisation, and medication status did not contribute significantly to the model. Similarly, severity (i.e. HRSD) number of episodes and length of period since first episode did not correlate with rCBF.
Videbech, et al., (2002) [2]	Depressed (42) vs. Controls (47)	PET with ^{15}Oxygen	Patients exhibited increased blood flow to the hippocampus, cerebellum, AC gyrus, and the basal ganglia compared to controls.	Strong negative correlation between the extent of psychomotor retardation and blood flow in the dorsolateral and supraorbital prefrontal cortices. Severity of depression (i.e. HRSD) was correlated with blood flow in the hippocampus.
Wu, et al., (1992)	Depressed (15) vs. Controls (15)	PET with ^{18}FDG – i.e. effect of sleep deprivation on brain metabolism in depression	After sleep deprivation 4 depressed patients showed reduced HRSD scores – i.e. 'responders'. Prior to sleep deprivation depressed responders exhibited significantly higher metabolic rate in the cingulate cortex than non-responders, this normalised after deprivation.	N/A

Appendix 1D: Summary of functional activation studies of depression

Note: Unless otherwise noted the studies selected examine cortical activation in individuals with major depression (i.e. 'Depressed') compared to normal healthy controls ('Controls') during the performance of the specified cognitive task. Where alternative participant groups were employed then this is explicitly noted. However, only those results relevant to the pattern of cortical function in unipolar depressive illness are noted.

Author(s) (date)	Participants: Type (N)	Method	Cognitive function(s) of interest: Task	Conclusion(s)
Baker, Frith, & Dolan (1997)	Controls (10) – i.e. mood induction study	PET with ^{15}Oxygen	Verbal fluency: paced orthographic verbal fluency or word repetition	*Functional*: Activation was severely attenuated in the left prefrontal, premotor, and cingulate cortex and thalamus during performance of the verbal fluency task in the mood induction conditions. Attenuation of anterior cingulate activation was specific to depression. *Behavioural*: Not presented
Barch, et al., (2003)	Depression (14) vs. Schizophrenic (38) vs. Controls (49)	BOLD fMRI – block design	Working memory: 2-back task (i.e. both words and faces)	*Functional*: Individuals with depression, compared to schizophrenic patients, showed clear activation of the left and right DLFPC as well as bilateral activation of the inferior and superior frontal cortices during performance of the WM task. Controls demonstrated significantly higher activation that depressed patients in bilateral thalamus, right precentral gyrus, and right parietal cortex for both words and faces. In addition, controls showed significant task related activation for words but not faces in the right middle-temporal gyrus and right superior frontal gyrus, patients showed the opposite pattern. *Behavioural*: Depressed participants did not differ significantly from controls on performance on the 2-back task.

Author(s) (date)	Participants: Type (N)	Method	Cognitive function(s) of interest: Task	Conclusion(s)
Berman, et al., (1993)	Depressed (10) vs. Schizophrenic (10) vs. Controls (20)	^{133}Xenon inhalation – i.e. during 3 conditions: (1) resting state, (2) simple sensorimotor task, (3) cognitive task	Set-formation, set-maintenance, and set-shifting: WCST	*Functional*: No global or regional flow differences between the patients and controls under any of the testing conditions. There was, however, a significant difference between the laterality indices of controls and patients for the parietal regions during performance of the WCST, i.e. while 75% of controls had relatively more blood flow to the left, 70% of patients showed more to the right. *Behavioural*: There was no significant difference between patients and controls on any of the measures of the WCST.
Elliot, et al., (1997)	Depressed (6) vs. Controls (6)	PET with ^{15}Oxygen	Planning: TOL	*Functional*: While controls engaged a network of prefrontal cortex, anterior cingulate, posterior cortical areas and subcortical structures (incl. the striatum), depressed patients failed to show significant activation in the cingulate and striatum, and activation in other prefrontal and posterior regions was significantly attenuated relative to controls. Patients failed to show the normal augmentation of activation in the caudate nucleus, anterior cingulate, and right prefrontal cortex associated with increase task difficulty. *Behavioural*: Depressed patients were impaired on the task compared to controls with regards to accuracy. Patients also experienced a disproportionate increase in difficulty in performance with increased task difficulty. However, depression had no effect on response latency

Author(s) (date)	Participants: Type (N)	Method	Cognitive function(s) of interest: Task	Conclusion(s)
Elliot, et al., (1998)	Depressed (6) vs. Controls (6)	PET with ^{15}Oxygen	Planning: TOL (vs. 'guessing' task) – under 3 feedback conditions: (1) positive (2) negative, and (3) neutral	*Functional*: Compared with controls, depressed patients failed to show significant activation in the medial caudate and the ventromedial OFC. Activity in the depressed group was overall lower and they did not show the differential response associated with condition that was observed in controls. *Behavioural*: Depressed patients performed less accurately overall compared to controls. Both groups performed less accurately in the negative feedback condition than in the positive condition. In the neutral condition while the performance of controls was most similar to the positive condition the performance of depressed patients was similar to the negative feedback condition.
Kaiser, et al., (2003)	Depressed (16) vs. Controls (16)	High resolution ERP	Executive control, i.e. response inhibition: auditory Go/No-go task	*Functional*: Both groups showed the same voltage pattern in the 'Go' task, but in the 'No-go' task depressive patients showed a reduction of the early fronto-temporal positivity in the N2 time window, which was associated with response inhibition in controls. Suggests a dysfunctional activation of the network subserving executive control during an early stage of cortical processing. *Behavioural*: Depressed patient performed as well as controls in the 'Go' conditions, but were impaired on the 'No-go' condition (i.e. response inhibition)
Kimbrell, et al., (2002)	Depressed (38: range from euthymic – severely depressed (i.e. HRSD ≥ 22)) vs. Controls (37)	PET with ^{18}FDG – i.e. measuring regional cerebral glucose metabolism (rCMRglu)	Sustained attention: auditory continuous performance test	*Functional*: Severely depressed patients showed decrease rCMRglu in the right PFC and paralimbic/amygdala regions and bilaterally in the insula and temporoparietal cortex (right > left); they also exhibited increased normalised metabolic activity bilaterally in the cerebellum, lingula/cuneus and brain stem. *Behavioural*: Performance of depressed patients and controls was similar on the task with regards to the hit rate, false alarm rate, and miss rate. However, the reaction times of depressed patients were significantly slower than controls. *Factors of interest*: Severity of depression (i.e. HRSD) was negatively correlated with absolute rCMRglu in almost the entire extent of the right cingulate cortex, and bilaterally in PFC, insula, basal ganglia, and temporoparietal cortex (right > left).

Author(s) (date)	Participants: Type (N)	Method	Cognitive function(s) of interest: Task	Conclusion(s)
Knott & Lapierre (1987)	Depressed (21) vs. Controls (21)	Cortical EP and integrated electromyogram (EMG)	Psychomotor response: choice reaction time (visual)	*Functional*: Compared to controls patients exhibited delayed EMG latencies and attenuated EP amplitudes. *Behavioural*: Depressed patients were found to exhibit an overall slower RT than controls, including measures of decision time, movement time and total time (i.e. decision + movement time). *Factors of interest*: No correlation between depression severity (i.e. HRSD) and any of the behavioural or electrophysiological measures.
Kumari, et al., (2003)	Depressed (6) vs. Controls (6)	BOLD fMRI – block design	Cognitive generation of affect – i.e. using affectively positive and negative picture-caption pairs	*Functional*: Compared to controls, patients showed relatively decreased response in the AC (rostral: right), with both negative and positive picture-caption pairs, and in the medial frontal gyrus and the hippocampus (left in both cases) with positive picture-caption pairs. Increased response in patients was seen in the inferior (right) and middle (left) temporal gyri with negative picture-caption pairs, and in the parahippocampal gyrus (right), inferior frontal gyrus (left), subgenual cingulate gyrus (right), striatum (right), and brain stem (left) with positive picture-caption pairs. *Behavioural*: No effect of group, and no group x valence interaction on the picture-caption task.
Okada, et al., (2003)	Depressed (10) vs. Controls (10)	BOLD fMRI – block design	Verbal fluency	Functional: Activation in depressed participants was attenuated in the left PFC, and they failed to show significant activation in the left prefrontal cortex, such as was seen in the controls. Behavioural: Depressed patients were significantly impaired on the verbal fluency task compared to controls

Author(s) (date)	Participants: Type (N)	Method	Cognitive function(s) of interest: Task	Conclusion(s)
Pelsoi, et al., (2000)	Depressed (14) vs. Controls (14)	EEG	Working memory - Sternberg working memory task	*Functional*: Patient's event related potentials differed significantly from controls. Pathological changes were similar for visual and auditory presentation. Abnormalities were suggestive of abnormal sensory/perceptual processing in modality-specific association cortices, possibly due to a failure of selective attention, and of activation of additional neuronal assemblies than those normally participating in the task, which may reflect either compensatory mechanisms or dysfunction of inhibitory systems. Given that the changes were sensitive to memory load suggests that they reflect alterations of memory-related processes. *Behavioural*: Patients made more mistakes than controls as memory load was increased from one to five digits.
Videbech, et al., (2003)	Depressed (41) vs. Controls (46)	PET - ^{15}Oxygen	Verbal fluency	*Functional*:: Both patients and controls activated left AC, left DLPFC, left medial PFC, and right cerebellum during performance of the task. However, there were no significant differences in the pattern of activation between patients and controls. *Behavioural*: Depressed patients were significantly impaired on the verbal fluency task compared to controls

Appendix 1E: Summary of metabolic functional neuroimaging studies of working memory

Notes: [1] Unless otherwise stated all samples consisted of adult participants; [2] fMRI investigations only; * - This study examined the reproducibility of fMRI data across four sites. Two participant groups were formed for the analyses, i.e. Group 1 = data from 2 participants from each site, N = 8; Group 2 = data from 5 – 8 participants from each site, N not specified.

Key:
normal – neurologically normal
RH – right handed
LH – left handed
VWM – verbal working memory
SWM – spatial working memory
nVWM – non-verbal working memory
nSWM – non-spatial working memory
DMTS – delayed match-to-sample
NS – not specified

Author(s), date	Participants (N): Definition, male: female [1]	Imaging technique: analysis method [2]	WM function: modality, Task	Key findings & regions of interest
Barch et al., 1997	11: normal, RH, 7:4	BOLD fMRI – block design	VWM: AX-CPT	Increased activity in the DLPFC during task conditions that placed demand on active maintenance relative to control conditions matched for difficulty. In addition, this activity was sustained and did not increase over the retention interval when task difficulty was manipulated independently. Transient increases were noted in the AC in response to increased difficulty but not WM demands – i.e. evidence of double dissociation between regions responsive to WM vs. task difficulty.

Author(s), date	Participants (N): Definition, male: female [1]	Imaging technique: analysis method [2]	WM function: modality, Task	Key findings & regions of interest
Braver et al., 1997	2 studies: (1) 9: normal, RH, 8:1 (2) 8: normal, RH, 6:2	BOLD fMRI – block design (2) whole-brain imaging	(1) VWM: visual, N-back (0- → 3-back) (2) same paradigm, but shorter block duration & fewer trials of each level	(1) Linear relationship with memory load noted in the middle frontal gyrus (MFG; BA 46/9) bilaterally, the left inferior frontal gyrus (LIFG; BA 44/45), a more anterior left inferior site (BA 47/10), and the anterior cingulate gyrus (AC; BA 32). However, planned comparisons revealed monotonic change in MFG and LIFG only – i.e. a linear relationship between signal and load in both regions. Similar findings for analysis of relationship between RT (i.e. independent measure of memory load) and signal change. (2) Same pattern of activation the MFG & LIFG. Also load-sensitive activity in the right homologue of LIFG (BA 44), left frontal operculum (insular cortex), and a number of motor, premotor, and supplementary motor regions (BA 4 & 6). Nonfrontal activity in bilateral posterior parietal cortex (BA40/7) and left caudate nucleus
Callicott et al., 1999	9: normal, NS, 6:3	BOLD fMRI – block design	SWM: visual, N-back (0- → 3-back)	Increased load associated with declined accuracy. Load sensitive responses in a distributed network that included DLPFC (BA 9-10/44-46), premotor cortex (BA6/8), a pericingulate region covering the medial frontal gyrus (supplementary motor area (SMA), medial BA 6) and AC (BA 32), the basal ganglia & thalamus, and parietal cortex (BA 7, 39-40). Evidence of laterality, i.e. bilateral DLPFC activation, greater no. of right DLPFC foci, and both dorsal (BA 9/46) and ventral (BA 6/8) areas. Loci in DLPFC evinced U-shaped response to linear increase in difficulty.
Casey et al., 1998	Normal * (NS)	BOLD fMRI – block design	SWM: visual, N-back (0- & 2-back)	Performance of the SWM task was reliably associated with activity in the right DLPFC & right superior parietal lobule in data across all four sites sampled in this study.
Cohen et al., 1994	12: normal, RH, 7:5	BOLD fMRI – block design	VWM: visual, DMTS	Reliable activation in the middle and inferior frontal gyri in performance of the WM task relative to the control task. Time course of increases and decreases in activation was consistent with the task manipulations.

Author(s), date	Participants (N): Definition, male: female [1]	Imaging technique: analysis method [2]	WM function: modality, Task	Key findings & regions of interest
Cohen et al., 1997	10: normal, NS, 5:5	BOLD fMRI – block design	VWM: visual, N-back (0- → 3-back	Strong effect of time but not memory load in visual, motor, and somatosensory cortex. Regions sensitive to memory load included DLPFC, more posterior and inferior regions of PFC (including Broca's area), and posterior parietal cortex. Activation in DLPFC associated with load but not time. Similar pattern observed in more posterior regions including Broca's area (BA 44) and posterior parietal cortex (BA 40) – but in posterior areas they co-occur with other regions that show time and load associations. Effect of load in PFC appeared as a step function, i.e. activation increased primarily between 1- & 2-back conditions.
D'Esposito et al., 1998	16: normal, RH, 10:6	BOLD fMRI – block design	VWM & SWM: N-back (0- & 2-back)	Similarly located activation in right MFG (BA 46) in both spatial and non-spatial tasks, i.e. no evidence of dorsal/ventral dissociation in PFC function associated with WM subtype.
D'Esposito et al., 1998	8: normal, RH, 3:5	BOLD fMRI – block design	VWM & SWM: visual, N-back (0- & 2-back)	Working memory tasks resulted in greater prefrontal activation than a non-WM task. Non-WM task caused greater activation in the same regions compared to 'rest' condition. Concluded that lateral prefrontal cortex supports processes in addition to WM.
Diwadkar, Carpenter & Just, 2000	2 studies: (1) 18: normal, RH, NS (2) 8: normal, RH, NS	BOLD fMRI – block design	(1)SWM: visual, DMTS. 2 factors of interest, i.e. 2D vs. 3D objects & no. of object to be remembered (1 vs. 3). (2) Same visual task as (1), plus auditory presentation of stimuli.	(1) Activation of DLPFC and parietal cortex varied as a function of the number of object locations to be remembered and the dimensionality of the object(s). Analysis of response characteristics in individual voxels revealed that a large proportion were activated only during higher level of demand of both variables. A smaller number were activated specifically in response in task demand associated with a specific variable. (2) Same effect of dimensionality in the parietal cortex when the movement of objects was presented auditorily rather than visually - i.e. additional representational demands induced by 3D space are independent of input modality. Co-modulation of activation in PFC and parietal cortex by the level of computational demand is indicative of collaboration between these regions, which may underlie the functionality of SWM.

Author(s), date	Participants (N): Definition, male: female [1]	Imaging technique: analysis method [2]	WM function: modality, Task	Key findings & regions of interest
Glabus et al., 2003	39: normal, RH, 22:17	BOLD fMRI – block design (using structured equation modelling)	VWM: visual, N-back (0- & 2-back)	Group model consisted principally of regions in the prefrontal and parietal cortices, with considerable interindividual differences. High performers engaged a LH sub-network involving inferior parietal lobule and Broca's area. Low performers utilised a RH sub-network with interactions between inferior parietal lobule and DLPFC. Thus better performance appears to be associated with engaging neural systems associated with verbal processing. Moreover, interaction between parahippocampal gyrus & inferior parietal lobule related to different strategies.
Honey, Bullmore & Sharma, 2000	20: normal, RH, all male	BOLD fMRI – block design	VWM: visual, N-back (0- & 2-back)	Performance of N-back task activated a distributed network, including DLPFC, inferior frontal gyrus, lateral premotor cortex, and SMA in the frontal lobes. Also, major foci of activation in more posterior regions, including regions in both parietal and occipitoparietal cortex, precuneus, lingual and fusiform gyri of the ventral occipital lobe, inferior temporal gyrus, and cerebellum. Level of activation in bilateral posterior parietal cortex was positively correlated with RT. This latter finding is consistent with those studies that have identified similar areas of parietal cortex as the site of the phonological store.
Isoardi et al., 1999	9: normal, NS, NS	^{15}O PET (EXACT HR+)	VWM: visual, N-back (0- → 3-back)	Activated brain regions were identified in he DLPFC, bilaterally, the bilateral parietal and cerebellar cortices and the AC. By varying the dose level of ^{15}O (i.e. 5, 10 & 15 mCi) this study demonstrated that peak count rate is approached at around 15 mCi, but that robust activation maps can be obtained with as little as 5 mCi.

Appendix Two: Materials

Appendix 2A: Recruitment materials

1. Information sheet for medical staff: Experiments One & Two
2. Patient recruitment advertisement: Experiments One & Two
3. Control recruitment advertisement: Experiments One & Two
4. Information sheet for participants: Experiments One & Two
5. Consent from: Experiments One & Two
6. Information pack: Experiment Three
    a. Exclusion criteria list
    b. Information sheet for participants
    c. Medication information sheet
    d. Statement on compensation arrangements
    e. Consent form
    f. GP information sheet
    g. Personal details form
7. GP Letter: Experiment Three

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Research project: Working Memory in Depression

Information sheet for medical staff

We are currently trying to recruit patients with major depression to take part in a study looking at working memory deficits in depression and their underlying causes (the details of which have already been presented to and reviewed by the Lothian Psychiatry/Clinical Psychology Research Ethics Committee).

There are two phases to this study. In the pilot phase patients are asked to attention the Royal Edinburgh to complete a number of behavioural, affective, and neuropsychological tests, in order to assess the severity of depression and the level of cognitive impairment. In the second experimental phase, we are asking patients to attend the Western General Department of Clinical Neurosciences Unit, where they will be asked to complete a working memory tasks while have a functional MRI can. Participation in either phase is expected to take approximately 1 ½ hours. We have already begun conducting the pilot study and it is expected that the first experimental trials will run sometime between now and early next year.

We are presently looking for a further 15 patients to participate in the pilot phase , and an additional 10 patients to take part in the experimental trials. We are hoping to recruit patient already receiving in- or out-patient care for depression, or those who have only recently been referred to outpatient services. It is expected that patients who wish to participant will fulfil the following inclusion criteria:

1. Aged between 18 and 50 years old
2. No history of head injury
3. No previous neural surgery
4. No history of diabetes, liver disease, heart attacks, strokes, or other major physical illness
5. Not colour blind
6. Not currently pregnant
7. No recent alcohol or drug abuse
8. No ECT in the last six months
9. No change in medication within the last week (including changes in dose)
10. No history of psychotic symptoms

It is essential that we meet with patients prior to them taking part in order to discuss the study and what would be expected of them. All patients who wish to participate in this study will be provided with an information sheet a minimum of 48 hours prior to participation. They will be advised to discuss participation with both their families and their physician. They will also be advised that they are free to withdraw at any stage.

Any questions regarding participation, from both staff and patients, can be directed to either Prof. Klaus Ebmeier or myself at the above address
Emma Jane Rose (Clinical supervisor: Prof. K. Ebmeier)

Emma Jane Rose
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Email: e.j.rose@sms.ed.ac.uk

Working Memory in Depression: an fMRI study

Patient Recruitment

Prof. Klaus Ebmeier and myself area currently conducting a study looking at cognitive and functional brain deficits in major depression

We are looking for individuals with a diagnosis of major depression to take part in this study, who meet the following criteria:

11. Aged between 18 and 50 years old
12. No history of head injury
13. No previous neural surgery
14. No history of major physical illness
15. No recent alcohol or drug abuse
16. No ECT in the last six months
17. No change in medication within the last week (including changes in dose)
18. No history of psychotic symptoms

This study is being conducted in two phases. The first involves completion of a couple of assessments of mood, two short tests of attention, and a computerised working memory task. The second phase involves completion of the memory task, while undergoing a functional MRI scan. Participation in either phase is expected to last between 1 – 1 ½ hours.

All patients who wish to participate will be provided with an information sheet a minimum of 48 hours prior to taking part, and given the opportunity to ask any questions they may have regarding participation.

If you are aware of any patients who may be suitable to participate, or have any questions regarding the study, please contact either Prof. Ebmeier or myself. You can telephone me internally on ext. 46802 or page me on 5682

Thank you

Emma Jane Rose
MRC PhD Student
Department of Psychiatry
(Clinical supervisor: Prof. K. Ebmeier)

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Working Memory in Depression: an fMRI study

Volunteers Needed

Prof. Klaus Ebmeier and myself area currently conducting a study looking at cognitive and functional brain deficits in major depression and are currently in need of healthy volunteers to participate as controls in this study.

The study is being conducted in two phase. The first involves completion of a couple of questionnaires relating to mood, two short tests of attention, and a computerised working memory task. The second phase involves completion of the working memory task while undergoing a functional MRI scan.

19. Aged between 18 and 50 years old
20. No history of head injury
21. No previous neural surgery
22. No history of major physical illness
23. No history of mental health problems

If you, or anyone you know, meets the above criteria and would be interested in participating the study please let me know. Similarly if you have any questions regarding the study please feel free to contact me. I can be contact on the above number, or on the internal exchange at the Royal Edinburgh Hospital on ext. 46802 or pager number 5682

Thank you

Emma Jane Rose
MRC PhD Student
Department of Psychiatry
(Clinical supervisor: Prof. K. Ebmeier)

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Tel & Fax: +44-131-537-6505

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish. Ask us if there is anything that is not clear of if you would like more information. Take time to decide whether or not you wish to take part.
Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to aask. A copy may be obtained from CERES, PO Box 1365, London, N16 0BW.

Thank you for regarding this.

Working Memory in Depression

What is the purpose of this study?
People who are depressed often report that they have memory and attention difficulties in everyday situations, particularly if it is necessary to keep track of some sorts of information and ignore others. For example, holding in mind directions about a route whilst ignoring a radio program. Only a small amount of research has been directed at understanding these sorts of problems in depression.
Why have I been chosen?
You will either be one of 20 patients who have been in contact with the hospital or outpatient clinic and have been diagnosed as suffering from a major depressive episode, or one of 20 healthy volunteers studied in the control group.
Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive as a patient.
What will happen to me if I take part?
If you would like to be included in this study, you will be invited to the University Department of Psychiatry at the Royal Edinburgh Hospital fro about an hour. In addition to having a go at the memory task you will be asked to answer questions about your medical history and fill out some short questionnaires about how you are feeling at the moment. In this study, we would like to find out under what circumstances people with depression find it difficult to keep track of information. To do this we will ask you to have a go at a computerised memory task in which you be asked to keep in mind particular place on a computer screen and respond by button pressing. We will adjust the difficulty of the task by varying how long you need to keep this information in mind. The point of this study is to define the range of difficulty coped with by depressed and not depressed people.

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What are the possible side effects, risks or disadvantages of taking part and what happens if something goes wrong?
We do not anticipate that any harm could come to you as a result of participating, but if there is a problem, the Lothian Primary Care Trust is responsible for negligent harm, while the University of Edinburgh is insured against accidental injury.

What are the possible benefits of taking part?
Although we do not expect that any benefits will come to participants, it is hoped that your participation will be of benefit to those suffering from depression in the future.

Will my taking part in the study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The results will be published in a form that makes it impossible to identify individuals.

Who is organising or funding the research?
This research is organised by the Department of Psychiatry, University of Edinburgh, funded by the Scottish Higher Education Funding Council, and your doctor will not be paid for including you in the study.

Who has reviewed this study?
This study has been reviewed by the Lothian Psychiatry/Clinical Psychology Research Ethics Subcommittee.

Contact for further information:
K P Ebmeier, Professor of Psychiatry and Consultant Psychiatrist, Royal Edinburgh Hospital, Tel: 0131-5376526

Independent advisor:
Dr D Cunningham Owens, Reader in Psychiatry, Department of Psychiatry, Kennedy Tower, Royal Edinburgh Hospital (Tel: 0131-5376000)

Thank you for taking part in this study. You will be given a copy of this Information Sheet and a signed Consent Form to keep.

Department of Psychiatry
Kennedy Tower
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Edinburgh
EH10 5HF

Tel & Fax: +44-131-537-6505

Consent form

Research Project: Working Memory in Depression

Researcher: Prof. Klaus Ebmeier

Participant identification number: _____

Please read each of the following statements and initial the corresponding box:

	Initial box
I confirm that I have read and understood the information sheet for the above study and had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my future medical care or legal rights being affected.	☐
I understand that responsible persons from the University of Edinburgh and the University of Strathclyde may examine sections of my medical notes.	☐
I agree to take part in the above study.	☐

_____	/ /	_____
Name of patient	**Date**	**Signature**
_____	/ /	_____
Name of researcher	**Date**	**Signature**

3 copies to be made: 1 for patient; 1 for researcher; and 1 for hospital notes

Division of Psychiatry
School of Molecular and
Clinical Medicine
University of Edinburgh
Kennedy Tower
Royal Edinburgh Hospital
Morningside Park
EDINBURGH

Escitalopram and working memory

In order to take part in this study you must meet the following criteria:

1. Aged 18 – 50 years
2. No history of psychiatric illness
3. No history of serious physical illness – e.g. heart attack, stroke, diabetes, liver disease etc.
4. No previous serious head injury
5. Not colour blind
6. Not currently pregnant
7. No history of drug or alcohol addiction or serious abuse
8. No metallic implants e.g. pacemaker
9. Right-handed

Division of Psychiatry
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Kennedy Tower
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Information Sheet

Research Project: Escitalopram and working memory

Researchers: Prof K. Ebmeier and Emma Jane Rose

You are being invited to participate in the above research project. Before you decide whether or not to take part it is important for to understand why the research is being done and what it will involve. Please take the time to read the following information carefully, and discuss it with other if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

When people are depressed they are often prescribed an anti-depressant medication. These medications work on levels of two different neurotransmitters in the brain, i.e. serotonin and noradrenalin, which are implicated in mood and attention. In healthy volunteers anti-depressant medications appear to affect attention and concentration. The purpose of this study is to look at the effects that a selective serotonin reuptake inhibitor (SSRI), i.e. escitalopram, has on the ability of healthy volunteers to perform certain short-term memory and attention tasks.

Why have I been chosen?

You are one of a number of healthy individuals who have been approached to take part in the study.

Do I have to take part?

Participation in the study is entirely voluntary. If you decide to take part in the study you are still free to withdraw at any time, without giving a reason.

What will happen to me if I take part?

If you decide to take part in the study you will be invited to the University Department of Psychiatry for an initial interview, where you will be asked some questions regarding your medical history and fill out some questionnaires about your current mood. You will then be allocated to one of two groups. Individuals in group one will be asked to complete a computerised memory task, while undergoing a functional MRI scan. This type of scan allows us to see which parts of the brain become active while you complete the task. These individuals will then be asked to take 10mg of escitalopram/day for the next 7 days. After this you will be invited back to complete the same memory task again in the scanner. Individuals in group 2 will initially be prescribed 10mg escitalopram/day for 7 days; they will then undergo a scan while completing the task. Individuals in this group will then be invited to return for a second scan 7 days after they cease taking the medication. In addition after taking the medication for 7 days a sample of you blood will be taken in order that we can check the levels of the anti-depressant.

You will also be asked to provide a blood sample on the day that you commence the antidepressant treatment, and on the final day of the course of medication.

What are the possible side effects, risks or disadvantages of taking part, and what happens if something goes wrong?

You may suffer some side effects while you are taking these drugs. We expect these to be mild. In some individuals escitalopram can cause nausea, headache, dizziness, insomnia, agitation, nervousness, constipation, diarrhoea, palpitation, dry mouth, sleepiness, weakness, increased sweating or tremor. Some individuals also find that their concentration is altered. Given this possibility we do not recommend that you take part if you are about to undergo any important examinations. We expect that any side effects you may experience will be mild and we do not expect that any harm could come to you as a result of taking part. However, if there is a problem Lothian Primary Care Trust is responsible for negligent harm, while the University of Edinburgh is insured against accidental injury. There will be an available contact on the research team 24 hours a day 7 days a week if there are any questions or problems. Your general practitioner will also be informed about your participation and will be able to contact the research team if the study code needs to be broken.

What are the possible benefits of taking part?

While we do not anticipate any direct benefits to the participants of this study, it is hoped that your participation will be of benefit to those individuals suffering from depression.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which is collected will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results of the study will be published in a form that makes it impossible to identify individuals who took part in the project. After the study is completed your information will be kept by the Department of Psychiatry and may be used again in the future for other research projects.

Who is organising or funding the research?

This research is organised by the Department of Psychiatry, University of Edinburgh, and is funded by the Scottish Higher Education Funding Council, and the Medical Research Council.

Contact for further information:
Prof K. Ebmeier, Professor of Psychiatry and Consultant Psychiatrist, Royal Edinburgh Hospital, Tel: 0131 537 6505
or
Ms Emma Jane Rose, MRC PhD Student, Department of Psychiatry, Royal Edinburgh Hospital, Tel: 0131 537 6802

Independent advisor:
Prof D Blackwood, Professor of Psychiatry, University of Edinburgh, Kennedy Tower, Royal Edinburgh Hospital, Tel: 0131 537 6000

Thank you for taking the time to read this. If you decide to take part in this study you will be given a copy of this information sheet and a signed consent form to keep.

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Royal Edinburgh Hospital
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Medication Information Sheet

Research project: Escitalopram and working memory

Escitalopram is an antidepressant medication, which belongs to a class of drugs known as selective serotonin reuptake inhibitors (SSRI's). As with all medications, escitalopram has a number of reported potential side effects.

The following table indicates the percentage of patients with depression who experienced the most common side effects associated with use of escitalopram, and how these figures compared with individuals who where prescribed a placebo (i.e. a 'dummy' medication)

**TABLE 1 - TREATMENT-EMERGENT ADVERSE EVENTS*
INCIDENCE IN PLACEBO-CONTROLLED CLINICALTRIALS**

Body System/Adverse Event	Percentage of Patients Reporting	
	Escitalopram (n=715)	Placebo (n=592)
Dry Mouth	*6%*	*5%*
Nausea	*15%*	*7%*
Fatigue	*5%*	*2%*
Increased Sweating	*5%*	*2%*
Somnolence	*6%*	*2%*
Insomina	*9%*	*4%*
Ejaculation disorder	*9%*	*<1%*

(from www.lexapro.com, accessed 25/10/2002)

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Statement on compensation arrangements

The University of Edinburgh holds a no-fault insurance clinical trials protection policy which provides compensation to a research subject in respect of accidental injury arising out of a clinical trial undertaken in the name of the university.

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Consent Form

Research Project: Escitalopram and working memory

Researchers: Prof. Klaus Ebmeier and Emma Jane Rose

Participant identification number: _____

Please tick box

I confirm that I have read and understood the information sheet for the above study and had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my future medical care or legal rights being affected.	☐
I agree for notice to be sent to my General Practitioner about my participation in this study,	☐
I agree to the provision of clinically significant information to my General Practitioner about my participation in this study.	☐
I understand that this is a non-therapeutic research project from which I cannot expect to derive benefit.	☐
I agree to take part in the above study.	☐

_____	/ _____ /	_____
Name of Patient	**Date**	**Signature**
_____	/ _____ /	_____
Name of researcher	**Date**	**Signature**

3 copies to be made: 1 for participant; 1 for researcher; 1 for GP

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Royal Edinburgh Hospital
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GP Information

In order that we can forward appropriate information to your GP please complete the details below. Thank you.

Your name:	
Name of GP:	
Surgery address:	
Surgery Tel:	

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Kennedy Tower
Royal Edinburgh Hospital
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Escitalopram and working memory

Please complete the following details and return it to me in the enclosed envelope, along with the other forms (i.e. consent form, GP information and availability forms):

Your name:	
Address:	
Tel:	
Email:	

Division of Psychiatry
School of Molecular and
Clinical Medicine
University of Edinburgh
Kennedy Tower
Royal Edinburgh Hospital
Morningside Park
EDINBURGH
EH10 5HF
Tel: 0131 537 6000

Dear Dr

RESEARCH PROJECT: The effect of escitalopram on working memory in healthy volunteers: A functional MRI Study

Your patient ..... has agreed to take part in the above research project. He/she will be asked to take 10 mg of escitalopram/day for 7 days. In addition he/she will be asked to complete a working memory task while undergoing a functional MRI scan. Participants will be scanned both on and off medication.

Your patient has already been screened for any history of psychiatric or serious medical illness. However, if you feel that there is any reason why he/she should not participate in the study please do not hesitate to contact us. Similarly, if at any point during the study you feel that he/she should be withdrawn from participation please let us know.

With this letter I have enclosed a copy of the information sheet for this project and a copy of your patients consent form.

If you have any queries please feel free to contact me.

Kind regards,

Emma Jane Rose

Clinical Supervisor: Professor Klaus Ebmeier.

Appendix 2B: Pre-test materials

1. Medical history questionnaire: Patients
2. Medical history questionnaire: Controls
3. Patient information sheet
4. Pre-scan questionnaire

Medical History: Patients

Please complete the following questionnaire by either filling in the boxes, or, where required, by ticking the appropriate box. Please be careful to answer all questions, and to answer each question truthfully. All information obtained will be treated confidentially.

Name: ☐

Date of Birth: ☐

Sex: Female ☐ Male ☐

Occupation: ☐

1. Have you ever suffered from any of the following conditions (please tick):

   Diabetes ☐

   Liver disease ☐

   Heart attack ☐

   Stroke ☐

   Any other major physical illness ☐
   (If yes, which illness _____)

2. Have you ever suffered a head injury (even mild)?

   Yes ☐ No ☐

3. Have you ever had any form of neural surgery?

   Yes ☐ No ☐

4. Are you colour blind?

   Yes ☐ No ☐

5. Are you currently pregnant?

   Yes ☐ No ☐

6. How many units of alcohol have you consumed in the last week? ☐

(Note: 1 unit = 125ml glass of wine, 25ml measure of normal strength spirit, or ½ pint of normal strength lager, beer or cider)

Does this indicate an average/normal week for you (i.e. your average consumption per week over the last three months)?

Yes ☐ No ☐

If no, how many units would you consume in an average/normal week?

☐

7. Are you currently taking any prescription medication?

   Yes ☐ No ☐ Medication/Dose _____

   If yes, are you taking this medication in accordance with your doctor's orders?

   Yes ☐ No ☐

   If no, describe _____

8. How long has it been since you were first diagnosed as suffering from depression?

   ☐

9. Have you ever received ECT as part of your treatment for depression

   Yes ☐ No ☐ Time since last ECT treatment: _____

10. Are you left or right handed? _____

Medical History: Controls

Please complete the following questionnaire by either filling in the boxes, or, where required, by ticking the appropriate box. Please be careful to answer all questions, and to answer each question truthfully. All information obtained will be treated confidentially.

Name: ☐

Date of Birth: ☐

Sex: Female ☐ Male ☐

Occupation: ☐

1. Have you ever suffered from any of the following conditions (please tick)?:

   Diabetes ☐

   Liver disease ☐

   Heart attack ☐

   Stroke ☐

   Any other major physical illness ☐
   (If yes, which illness _____)

2. Have you ever suffered a head injury (even mild)?

   Yes ☐ No ☐

3. Have you ever had any form of neural surgery?

   Yes ☐ No ☐

4. Are you colour blind?

   Yes ☐ No ☐

5. Are you currently pregnant?

   Yes ☐ No ☐

6. How many units of alcohol have you consumed in the last week? ☐

(Note: 1 unit = 125ml glass of wine, 25ml measure of normal strength spirit, or ½ pint of normal strength lager, beer or cider)

Does this indicate an average/normal week for you (i.e. your average consumption per week over the last three months)?

Yes ☐ No ☐

If no, how many units would you consume in an average/normal week?

☐

7. Are you currently taking any prescription medication?

   Yes ☐ No ☐

   If yes, are you taking this medication in accordance with your doctor's orders?

   Yes ☐ No ☐

   If no, describe _____

8. Have you ever been diagnosed as suffering from any psychiatric illness?

   Yes ☐ No ☐

9. Are you left or right handed? _____

Department of Psychiatry
Kennedy Tower
Royal Edinburgh Hospital
Morningside Park
Edinburgh
EH10 5HF

Tel & Fax: +44-131-537-6505

Patient Information Sheet

Patient Identification Number: _____

Name of person providing information: _____

Date: _____

1. How long has it been since the patient was first diagnosed as suffering from major depression? ☐
2. Has the patient ever been diagnosed as suffering from any psychotic symptoms?
   Yes ☐ No ☐
3. Has the patient ever been diagnosed are suffering from drug and/or alcohol abuse?
   Yes ☐ No ☐
4. Is the patient currently prescribed any medication?
   Yes ☐ No ☐ Medication/Dose: _____
5. Has the patient ever received ECT as a treatment for their depression?
   Yes ☐ No ☐

Working Memory in Depression: Pre-scan Questionnaire

Participant Code:	
Scan code:	
Date:	

		Yes	No
1.	Do you suffer from any heart disease or rhythm disorder?	☐	☐
2.	Have you had recent surgery of any type (within the last six months)?	☐	☐
3.	Have you had any operations to your head (e.g. vascular clips, a cochlear implant, or a shunt)?	☐	☐
4.	Have you ever had any metal fragments (e.g. shrapnel) in any part of your body?	☐	☐
5.	Have you ever had any metal fragments in your eyes?	☐	☐
6.	Do you now, or have you ever worked with metal and had an injury which required medical attention?	☐	☐
7.	Could you be pregnant?	☐	☐
8.	Have you had any metal implants (e.g. joint replacement, Harrington rods etc.)?	☐	☐
9.	Do you wear dentures, a dental plate, a brace, contact lenses, or a hearing aid?	☐	☐
10.	Do you suffer from diabetes or epilepsy?	☐	☐
11.	Do you have an IUCD or sterilisation clips?	☐	☐
12.	Do you have any metallic implants or foreign metallic objects in your body other than those mentioned above?	☐	☐

Appendix 2C: Affective assessments

1. Beck Depression Inventory
2. Stress Arousal Checklist
3. Alderley Park State Anxiety Questionnaire

Beck Depression Inventory

ID _____ **DATE**_____ **TIME** _____ **(AM/PM)**

1.	0	I do not feel sad
	1	I feel sad
	2	I am sad all the time and I can't snap out of it
	3	I am so sad or unhappy that I can't stand it
2	0	I am not particularly discouraged about the future
	1	I feel discouraged about the future
	2	I feel I have nothing to look forward to
	3	I feel that the future is hopeless and that things cannot improve
3	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2	As I look back on my life all I can see is a lot of failures
	3	I feel I am a complete failure as a person
4	0	I get as much satisfaction out of things as I used to
	1	I don't enjoy things the way I used to
	2	I don't get real satisfaction out of anything anymore
	3	I am dissatisfied or bored with everything
5	0	I don't feel particularly guilty
	1	I feel guilty a good part of the time
	2	I feel guilty most of the time
	3	I feel guilty all of the time
6	0	I don't feel I am being punished
	1	I feel I may be punished
	2	I expect to be punished
	3	I feel I am being punished
7	0	I don't feel disappointed in myself
	1	I am disappointed in myself
	2	I am disgusted with myself
	3	I hate myself
8	0	I don't feel I am any worse than anybody else
	1	I am critical of myself for my weakness' or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself but would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10	0	I don't cry anymore than usual
	1	I cry more now than I used to
	2	I cry all the time now
	3	I used to be able to cry, but now I cant cry even though I want to

11 0 I am no more irritated now than I ever am
1 I get annoyed or irritated more easily than I used to
2 I feel irritated all the time now
3 I don't get irritated at all by the things that used to irritate me

12 0 I have not lost interest in other people
1 I am less interested in other people than I used to be
2 I have lost most of my interest in other people
3 I have lost all of my interest in other people

13 0 I make decisions as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty in making decisions than I used to
3 I can't make decisions at all anymore

14 0 I don't feel I look any worse than I used to
1 I am worried that I look old or unattractive
2 I feel that there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly

15 0 I can work about as well as before
1 It takes extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can't do any work at all

16 0 I can sleep as well as usual
1 I don't sleep as well as usual
2 I wake up 1 – 2 hours earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

17 0 I don't get more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything

18 0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all anymore

19 0 I haven't lost much weight, if any, lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds
I am purposely trying to lose weight by eating less Yes..... No.....

20 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains, or upset stomach or constipation
2 I am very worried about physical problems and it is hard to think of much else
3 I am so worried about my physical problems that I cannot think of anything else

21 0 I have not noticed any change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

Stress Arousal Checklist

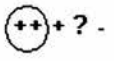
Name: _____

DEVELOPED BY
MACKAY, COX, LAZZERINI, AND BURROWS (1978)
REVISED BY COX AND MACKAY (1985)
MANUAL BY GOTTS AND COX (1987)

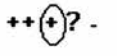
INSTRUCTIONS

The adjectives below describe different feelings and moods. Please use this list to describe your feelings at this moment in time.

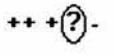
If the adjective definitely describes yours feelings circle the:



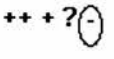
If the adjective more or less describes your feelings circle the:



If you do not understand the adjective, or you cannot decide whether it describes how you feel circle the:



If the adjective does not describe how you feel circle the:



Your first reactions will be the most reliable, therefore do not spend you too long thinking about each adjective. Please be as honest and accurate as possible.

Tense	++ + ?	Tired	++ + ?
Relaxed	++ + ?	Idle	++ + ?
Restful	++ + ?	Up tight	++ + ?
Active	++ + ?	Alert	++ + ?
Apprehensive	++ + ?	Lively	++ + ?
Worried	++ + ?	Cheerful	++ + ?
Energetic	++ + ?	Contented	++ + ?
Drowsy	++ + ?	Jittery	++ + ?
Bothered	++ + ?	Sluggish	++ + ?
Uneasy	++ + ?	Pleasant	++ + ?
Dejected	++ + ?	Sleepy	++ + ?
Nervous	++ + ?	Comfortable	++ + ?
Distressed	++ + ?	Calm	++ + ?
Vigorous	++ + ?	Stimulated	++ + ?
Peaceful	++ + ?	Activated	++ + ?

The Alderley Park State Anxiety Questionnaire (APSAQ)

Name: _____

Below are 12 statements
Please indicate to what extent each statement applies to you NOW.
For example, if at this moment you feel you can cope 'moderately' well please tick the column marked 'MODERATELY'

It is important to answer ALL 12 questions

Please tick one box only for each statement

		Not at all	Slightly	Moderately	Considerably	Extremely
1.	I feel I can cope	☐	☐	☐	☐	☐
2.	I am worried	☐	☐	☐	☐	☐
3.	I feel calm	☐	☐	☐	☐	☐
4.	I feel afraid	☐	☐	☐	☐	☐
5.	I want to escape from here	☐	☐	☐	☐	☐
6.	My body feels relaxed	☐	☐	☐	☐	☐
7.	My heart is beating faster	☐	☐	☐	☐	☐
8.	I can breathe freely	☐	☐	☐	☐	☐
9.	I have butterflies in my stomach	☐	☐	☐	☐	☐
10.	I feel sweaty	☐	☐	☐	☐	☐
11.	I can think clearly	☐	☐	☐	☐	☐
12.	My mind is racing	☐	☐	☐	☐	☐

Appendix 2D: Cognitive assessments

1. National Adult Reading Test
2. Rey Auditory Verbal Learning Test
    a. Form 1
    b. Recognition List: Form 1
    c. Form 2
    d. Recognition List: Form 2

NATIONAL ADULT READING TEST: WORD LIST

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FAÇADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DÉTENTE
EQUIVOCAL	IDYLL
NAÏVE	PUERPERAL
CATACOMB	AVER
GOALED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

The Auditory-Verbal Learning Test (AVLT Form 1)

Research Number .....

Participant Number ..... Date .....

Word List A	I	II	III	IV	V	Word List B	Recall	VI	Recog.
Violin						Orange			
Tree						Table			
Scarf						Toad			
Ham						Corn			
Suitcase						Bus			
Cousin						Chin			
Earth						Beach			
Stairs						Soap			
Dog						Hotel			
Banana						Donkey			
Town						Spider			
Radio						Money			
Hunter						Book			
Bucket						Soldier			
Field						Padlock			
Error									
Words									
Total									

Total = recall order
R = Repeated recall
RC = s corrects themselves
RQ = s unsure of item
E = error
EC = error (confabulation)
EA = error (association)

SCARF	TOAD	DONKEY	TRAIN
LEAF	CHIN	PEAR	UNCLE
STAIRS	HAM	COUSIN	VIOLIN
FROG	PIANO	GRASS	STARS
TABLE	FIELD	DOG	SPIDER
BANANA	SOAP	GLOVES	
HOSPITAL	TREE	HOTEL	
SUITCASE	CITY	BUCKET	
PEEL	HUNTER	SOFA	
BOOK	ORANGE	TOWN	
BLANKET	MONEY	BEACH	
PADLOCK	DOCTOR	CORK	
EARTH	SOLDIER	CORN	
TELEVISION	RADIO	LUNCHBOX	
ROCK	CHEST	BUS	

The Auditory-Verbal Learning Test (AVLT Form 2)

Research Number .....

Participant Number ..... Date .....

Word List A	I	II	III	IV	V	Word List B	Recall	VI	Recog.
Doll						Dish			
Mirror						Jester			
Nail						Hill			
Sailor						Coat			
Heart						Tool			
Desert						Forest			
Face						Perfume			
Letter						Ladder			
Bed						Girl			
Machine						Foot			
Milk						Shield			
Helmet						Pie			
Music						Insect			
Horse						Ball			
Road						Car			
Error									
Words									
Total									

Total = recall order
R = Repeated recall
RC = s corrects themselves
RQ = s unsure of item
E = error
EC = error (confabulation)
EA = error (association)

NAIL	HILL	FOOT	FLY
STALL	FOREST	BREAD	DART
BED	SAILOR	DESERT	DOLL
ENGINE	PONY	STREET	CAPTAIN
JESTER	ROAD	MACHINE	SHIELD
MILK	LADDER	JAIL	
SOOT	MIRROR	GIRL	
HEART	ENVELOPE	HORSE	
SILK	MUSIC	JOKER	
INSECT	DISH	LETTER	
SCREW	PIE	PERFUME	
CAR	SONG	PLATE	
FACE	BALL	COAT	
ARMOUR	HELMET	SAND	
HEAD	POOL	TOOL	

Appendix 3: Functional imaging results tables

Key to results tables:
LH: left hemisphere
RH: right hemisphere
LH/RH interhemispheric
BA: Brodmann area
K_E: cluster size (i.e. number of voxels, where each voxel = 8 mm^3)

Appendix 3A: Experiment Two: Block design significant activations (random effects)

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
Controls – within group	0 vs. 1	0 > 1	24 –66 2	RH	19	Lingual gyrus	664	< 0.001
			-14 –71 11	LH	23	Cuneus	1060	< 0.001
			10 –31 49	RH	6	Paracentral lobule	67	0.012
			16 41 44	RH	8	Superior frontal gyrus	68	0.011
			26 –82 24	RH		Middle occipital gyrus	114	< 0.001
			0 –17 40	LH	23	Cingulate gyrus	292	< 0.001
			-24 –56 –2	LH	19	Fusiform gyrus	73	0.007
			0 50 29	LH	9	Superior frontal gyrus	125	< 0.001
			-40 –40 –13	LH	37	Fusiform gyrus	59	0.023
Controls – within group	0 vs. 1	0 < 1	10 5 55	LH/RH	10/24	Medial frontal gyrus/cingulate gyrus	225	< 0.001
			-48 –24 55	LH	4	Postcentral gyrus	601	< 0.001
			28 7 60	RH	6	Middle frontal gyrus	242	< 0.001
			8 –56 54	RH	7	Precuneus	77	0.005
			-44 –41 44	LH	40	Inferior parietal lobule	299	< 0.001
Controls – within group	0 vs. 2	0 > 2	18 –40 –13	RH	19/37	Parahippocampal gyrus	341	< 0.001
			-38 –9 –23	LH	5	Paracentral lobule	7868	< 0.001
			-18 45 42	LH	8	Superior frontal gyrus	2192	< 0.001

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
			-8 28 56	LH	8	Superior frontal gyrus	112	0.003
			57 –13 6	RH	22/38	Superior temporal gyrus	2057	< 0.001
			16 38 53	RH	8	Middle frontal gyrus	106	0.005
			-48 –67 25	LH	21	Middle temporal gyrus	72	0.036
			6 32 13	RH	24	Anterior cingulate	72	0.036
			55 –65 27	RH	39	Middle temporal gyrus	104	0.005
Controls – within group	0 vs. 2	0 < 2	22 –71 53	RH	7	Precuneus	275	< 0.001
			28 7 59	RH	6	Medial frontal gyrus	303	< 0.001
			36 –54 49	RH	7	Superior parietal lobe	326	< 0.001
			46 34 26	RH	10	Middle frontal gyrus	75	0.03
			-44 –44 45	LH	40	Inferior parietal lobule	244	< 0.001
			-28 –1 55	LH	6	Precentral gyrus	85	0.016
Controls – within group	0 vs. 3	0 > 3	-4 –55 30	LH	31	Precuneus	1820	< 0.001
			-10 39 48	LH	8/9	Superior frontal gyrus	4275	< 0.001
			-28 –47 –8	LH	37	Fusiform gyrus	160	< 0.001
			18 –37 –10	RH	23	Posterior cingulate	282	< 0.001
			57 –5 15	RH	22/38	Superior temporal gyrus	341	< 0.001
			0 –30 64	LH/RH	6	Medial frontal gyrus	355	< 0.001

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
			-48 –67 29	LH	39	Middle temporal gyrus	135	0.001
			32 –28 62	RH	4	Precentral gyrus	160	< 0.001
			26 –93 5	RH	18/19	Occipital gyrus	102	0.006
			40 –21 16	RH	4	Post central gyrus	139	0.001
			44 –1 –23	RH	21	Middle temporal gyrus	227	< 0.001
			-6 –91 14	LH	18	Cuneus	265	< 0.001
			16 39 51	RH	8	Superior frontal gyrus	68	0.047
			12 –76 4	RH	18	Lingual gyrus	105	0.005
			24 34 –12	RH	11	Middle frontal gyrus	83	0.018
			51 –63 31	RH	39	Angular gyrus	73	0.034
			-28 –15 –19	LH	19/37	Parahippocampal gyrus	75	0.030
			46 –16 –8	RH	43	Insula	94	0.010
			-42 –16 -6	LH	43	Insula	90	0.012
Controls – within group	0 vs. 3	0 < 3	48 18 1	RH	47	Inferior frontal gyrus	108	0.004
			12 –69 55	RH	40	Superior parietal lobule	1482	< 0.001
			-28 1 55	LH	6	Middle frontal gyrus	336	< 0.001
			-38 55 5	LH	10/11	Middle frontal gyrus	96	0.009
			30 7 59	RH	6	Middle frontal gyrus	505	< 0.001

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
			-36 –60 49	LH	40	Superior parietal lobule	721	< 0.001
			40 55 6	RH	10	Middle frontal gyrus	94	0.010
			-48 4 38	LH	10	Middle frontal gyrus	65	0.057*
			-46 33 32	LH	9	Middle frontal gyrus	80	0.022
			6 22 47	RH	32	Medial frontal gyrus	159	< 0.001
Controls – within group	1 vs. 2	1 > 2	6 –59 23	RH	31	Posterior cingulate	1347	< 0.001
			14 47 –2	RH	24	Anterior cingulate	54	0.054*
			-10 59 23	LH	8	Superior frontal gyrus	535	< 0.001
			-28 –20 –16	LH	28	Parahippocampal gyrus	112	0.001
			14 –46 6	RH	31	Posterior cingulate	76	0.010
			-8 42 –9	LH	32	Medial frontal gyrus	103	0.001
			-28 –43 –10	LH	37	Parahippocampal gyrus	66	0.021
			-46 –64 33	LH	39	Angular gyrus	70	0.015
Controls – within group	1 vs. 2	1 < 2	20 –66 46	RH	7	Precuneus	355	< 0.001
			-30 –62 42	LH	7	Precuneus	71	0.014
Controls – within group	1 vs. 3	1 > 3	-2 –59 27	LH	31	Cingulate gyrus	730	< 0.001
			-12 49 5	LH	32	Medial frontal gyrus	370	< 0.001
			57 –13 3	RH	43	Superior temporal gyrus	384	< 0.001
			10 59 21	RH	9	Superior frontal gyrus	103	0.003

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	K_E	Significance ($p_{(corrected)}$)
			-4 37 2	LH	24	Anterior cingulate	62	0.047
Controls – within group	1 vs. 3	1 < 3	-36 21 –3	LH	47	Inferior frontal gyrus	148	< 0.001
			-38 49 7	LH	47	Middle frontal gyrus	155	< 0.001
			46 –47 41	RH	40	Inferior parietal lobule	1087	< 0.001
			40 19 –1	RH	47	Interior frontal gyrus	157	< 0.001
			-32 –58 42	LH	47	Superior parietal lobule	690	< 0.001
			48 36 28	RH	8	Middle frontal gyrus	738	< 0.001
			-30 1 53	LH	6	Middle frontal gyrus	123	0.001
			6 22 45	RH	8	Medial frontal gyrus	300	< 0.001
			34 53 5	RH	10	Middle frontal gyrus	205	< 0.001
			-42 0 37	LH	8	Middle frontal gyrus	71	0.025
Controls – within group	Increase	Increase	46 –46 45	RH	40	Inferior parietal lobule	1428	< 0.001
			-28 1 55	LH	6	Middle frontal gyrus	244	< 0.001
			28 6 48	RH	6	Middle frontal gyrus	458	< 0.001
			48 32 28	RH	10	Middle frontal gyrus	407	< 0.001
			-36 –60 49	LH	40	Superior parietal lobule	639	<0.001
			-36 51 7	LH	46	Middle frontal gyrus	144	0.001
			-46 33 32	LH	9	Middle frontal gyrus	79	0.028
			6 22 47	RH	8	Medial frontal gyrus	116	0.004

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
Controls – within group	Increase	Decrease	-4 –55 29	LH	31	Cingulate gyrus	2945	< 0.001
			-8 53 5	LH	11/8	Medial frontal gyrus	4461	< 0.001
			57 –5 15	RH	43	Precentral gyrus	1211	< 0.001
			-28 –47 –8	LH	37	Fusiform gyrus	158	< 0.001
			-48 –67 29	LH	21	Middle temporal gyrus	145	0.001
			42 1 –22	RH	22	Superior temporal gyrus	167	< 0.001
			-55 –25 5	LH	22	Superior temporal gyrus	94	0.012
			26 –45 –11	RH		Culmen	242	< 0.001
			30 –11 –23	RH	28/37	Parahippocampal gyrus	157	< 0.001
			-12 –94 18	LH	19	Cuneus	172	< 0.001
			-42 –18 –6	LH	43	Insula	224	< 0.001
			26 30 –17	RH	11	Middle frontal gyrus	80	0.026
			16 –89 15	RH	18	Middle occipital gyrus/cuneus	83	0.022
			51 –61 29	RH	22	Middle temporal gyrus	87	0.018
			-36 –15 –24	LH	37	Fusiform gyrus	104	0.007
			12 –74 4	RH	18	Lingual gyrus	94	0.012
Patients – within group	0 vs. 1	0 < 1	-26 –47 36	LH	40	Inferior parietal lobule	94	0.005
			-34 –46 48	LH	40	Inferior parietal lobule	68	0.027
Patients –	0 vs. 2	0 > 2	-18 –41 41	LH	5	Paracentral lobule	86	0.005

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	K_E	Significance ($p_{(corrected)}$)
within group			-4 50 –1	LH	10/32	Anterior cingulate	263	< 0.001
			59 –25 10	RH	40	Superior temporal gyrus	81	0.007
			-26 –35 –8	LH	28/37	Parahippocampal gyrus	98	0.002
			42 –6 –11	RH	43	Insula	72	0.013
			-4 –51 32	LH	7	Precuneus	129	< 0.001
Patients – within group	0 vs. 2	0 < 2	24 3 55	RH	6	Middle frontal gyrus	351	<0.001
			38 –42 44	RH	40	Inferior parietal lobule	864	<0.001
			-32 –52 45	LH	40	Inferior parietal lobule	744	<0.001
			38 37 11	RH	46	Middle frontal gyrus	209	<0.001
			-18 –48 –25	LH		Dentate	62	0.028
			46 12 –6	RH	47	Inferior frontal gyrus	61	0.031
			-8 –3 55	LH	6	Medial frontal gyrus	118	0.001
			4 –71 –12	RH		Declive	68	0.018
			-24 –3 54	LH	6	Precentral gyrus	183	< 0.001
Patients – within group	0 vs. 3	0 > 3	0 49 –1	RH	10	Medial frontal gyrus	760	< 0.001
			-6 –45 1	LH	28/37	Parahippocampal gyrus	86	0.011
			-44 –16 –6	LH	22	Superior temporal gyrus	145	< 0.001
			0 –58 14	LH	23	Posterior cingulate	774	< 0.001

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
			44 –10 –10	RH	21	Superior temporal gyrus	166	< 0.001
			-18 –41 41	LH	31	Cingulate gyrus	252	< 0.001
			-12 47 40	LH	8	Superior frontal gyrus	74	0.023
Patients – within group	0 vs. 3	0 < 3	28 3 55	RH	6	Middle frontal gyrus	450	< 0.001
			-28 –56 –29	LH		Pyramis/Declive	140	< 0.001
			36 36 22	RH	6	Middle frontal gyrus	131	0.001
			-24 –3 59	LH	6	Middle frontal gyrus	199	< 0.001
			46 –39 42	RH	40	Inferior parietal lobule	199	< 0.001
			-32 –52 45	LH	7	Superior parietal lobule	219	< 0.001
			-2 –59 56	LH	7	Precuneus	79	0.017
			38 –52 56	RH	40	Inferior parietal lobule	401	< 0.001
			14 14 49	RH	8	Superior frontal gyrus	102	0.004
Patients – within group	1 vs. 2	1 < 2	36 38 15	RH	10	Middle frontal gyrus	113	< 0.001
			-28 –54 43	LH	40/7	Superior and inferior temporal gyri	175	< 0.001
			28 –52 56	RH	40	Inferior parietal lobule	149	< 0.001
			26 8 51	RH	6	Middle frontal gyrus	74	0.007
Patients – within group	1 vs. 3	1 > 3	-2 –58 12	LH	30	Posterior cingulate	848	< 0.001
			-8 46 –12	LH	6	Medial frontal gyrus	119	< 0.001
			-50 –19 8	LH	41	Superior temporal gyrus	85	0.003

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	KE	Significance (p (corrected))
			-36 –4 6	LH	43	Precentral gyrus	125	< 0.001
Patients – within group	1 vs. 3	1 < 3	24 3 53	RH	6	Superior frontal gyrus	317	< 0.001
			32 –67 25	RH	7	Precuneus	151	< 0.001
			-24 –1 55	LH	6	Superior frontal gyrus	170	< 0.001
			-2 –61 56	LH	7	Precuneus	115	< 0.001
			24 –78 –5	RH	18	Lingual gyrus	78	0.005
			51 9 22	RH	46	Inferior frontal gyrus	51	0.05
Patients – within group	Increase	Increase	26 3 55	RH	6	Superior frontal gyrus	868	< 0.001
			40 5 24	RH	46	Inferior frontal gyrus	300	< 0.001
			50 –37 44	RH	40	Inferior parietal lobule	2817	< 0.001
			36 19 –3	RH	47	Inferior frontal gyrus	165	< 0.001
			-26 –52 –29	LH		Pyramis/Declive	229	< 0.001
			-22 –1 55	LH	6	Superior frontal gyrus	576	< 0.001
			36 36 22	RH	10	Middle frontal gyrus	412	< 0.001
			44 46 –4	RH	10	Middle frontal gyrus	99	0.004
			-26 –86 –4	LH	18	Lingual gyrus	60	0.055*
Patients – within group	Increase	Decrease	-4 51 1	LH	10	Medial frontal gyrus	1071	< 0.001
			-46 –12 –6	LH	22	Superior temporal gyrus	134	0.001
			-16 –41 43	LH	31	Posterior cingulate/precuneus	1270	< 0.001

Group-comparison	Contrast	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	K_E	Significance ($p_{(corrected)}$)
			42 –16 –1	RH	41	Transverse temporal gyrus	617	< 0.001
			22 –39 70	RH	4	Precentral gyrus	104	0.003
			4 –9 45	RH	24	Cingulate gyrus	157	< 0.001
			-48 –30 13	LH	41	Superior temporal gyrus	145	< 0.001
			-8 –47 1	LH		Culmen	83	0.012
			30 –79 –26	RH		Uvula/Pyramis	83	0.012
			61 –10 –13	RH	38	Middle temporal gyrus	108	0.002
			-20 –47 –11	LH		Culmen	66	0.036
Patients vs. Controls	0 vs. 2	$(0-2)_P - (0-2)_C < 0$	38 37 9	RH	46	Inferior frontal gyrus	141	0.010
			28 –34 66	RH	6	Medial frontal gyrus	619	< 0.001
			-12 –64 2	LH	18	Lingual gyrus	96	0.054*
			57 –4 4	RH	42	Superior temporal gyrus	160	0.005
			-12 –37 68	LH	43	Postcentral gyrus	98	0.050
Patients vs. Controls	0 vs. 3	$(0-3)_P - (0-3)_C < 0$	-12 44 -6	LH	12	Medial orbital prefrontal cortex/subgenual (rostral) anterior cingulate	164	0.006
Patients vs. Controls	1 vs. 2	$(1-2)_P - (1-2)_C < 0$	2 –83 10	RH	23	Cuneus	234	< 0.001
Patients vs. Controls	Increase	$(\text{Increase})_P - (\text{Increase})_C > 0$	-12 44 –6	LH	12	Medial orbital prefrontal cortex/subgenual (rostral) anterior cingulate	128	0.025

* = not significant but trend towards statistical significance.

Appendix 3B: Experiment two: Event related significant activations (random effects)

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
Controls – within group	0 correct	Increase	46 -37 52	RH	40	Inferior parietal lobule	135	< 0.001
			20 -43 -20	RH		Culmen	122	< 0.001
			40 -10 58	RH	6	Precentral gyrus	98	0.001
			-31 -8 56	LH	6	Precentral gyrus	103	0.001
			10 9 55	RH	6	Superior frontal gyrus	59	0.002
Controls – within group	0 correct	Decrease	20 -55 0	RH	18	Lingual gyrus	91	0.001
Controls – within group	1 correct	Increase	38 -10 56	RH	6	Middle frontal gyrus	195	< 0.001
			-23 -63 46	LH	7	Superior parietal lobule	182	< 0.001
			44 -35 52	RH	40	Inferior parietal lobule	110	< 0.001
			8 7 59	RH	6	Superior frontal gyrus	241	< 0.001
			-25 -3 46	LH	6	Middle frontal gyrus	429	< 0.001
Controls – within group	1 correct	Decrease	4 -20 42	RH	24	Cingulate gyrus	60	0.015
			-3 -44 35	LH	31	Cingulate gyrus	99	0.001
			-23 -54 -6	LH	28/37	Parahippocampal gyrus	61	0.014
			26 -63 2	RH	19	Lingual gyrus	114	< 0.001

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	KE	Significance (p (corrected))
			-3 56 27	LH	9	Superior frontal gyrus	55	0.024
			0 43 -3	LH/RH	24/11	Anterior cingulate/medial frontal gyrus	69	0.007
Controls – within group	2 correct	Increase	-21 -68 53	LH	7	Superior parietal lobule	275	< 0.001
			2 6 44	RH	6	Medial frontal gyrus	412	< 0.001
			46 -37 52	RH	40	Inferior parietal lobule	178	< 0.001
			51 13 32	RH	9	Middle frontal gyrus	66	0.016
			38 0 57	RH	6	Middle frontal gyrus	288	< 0 .001
			-29 -6 54	LH	6	Middle frontal gyrus	233	< 0.001
			-35 -38 37	LH	40	Inferior parietal lobule	101	0.001
Controls – within group	2 correct	Decrease	-19 34 52	LH	8	Superior frontal gyrus	200	< 0.001
			20 -49 1	RH	19	Lingual gyrus	79	0.006
			-27 -39 -16	LH	37	Parahippocampal gyrus	76	0.007
			-15 -95 14	LH	18	Middle occipital gyrus	124	< 0.001
			0 49 16	LH/RH	9/32	Superior frontal gyrus/anterior cingulate	305	< 0.001
			4 25 39	RH	6	Medial frontal gyrus	66	0.016
			-3 -46 34	LH	31	Precuneus	134	< 0.001
Controls – within group	3 correct	Increase	18 -43 -19	RH		Culmen/Declive	154	< 0.001
			38 -10 56	RH	6	Precentral gyrus	256	< 0.001

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			6 5 55	RH	32	Cingulate gyrus	668	< 0.001
			22 -72 52	RH	7	Precuneus	122	< 0.001
			-23 -65 44	LH	7	Superior parietal lobule	329	< 0.001
			-23 -3 46	LH	6	Middle frontal gyrus	415	< 0.001
			8 -55 51	RH	31	Precuneus	71	0.009
			50 -43 50	RH	40	Postcentral gyrus	165	< 0.001
			53 10 38	RH	8/6	Middle frontal and precentral gyri	66	0.074
			-35 -40 37	LH		Parietal lobe – sub-gyral	61	0.022
			-27 -54 -20	LH		Culmen/declive	59	0.026
Controls – within group	3 correct	Decrease	-9 47 40	LH	10	Superior frontal gyrus	1185	< 0.001
			12 32 54	RH	6/8	Superior frontal gyrus	90	0.002
			28 -54 -1	RH	19	Lingual gyrus	159	< 0.001
			-29 -39 -16	LH	20	Fusiform gyrus	111	< 0.001
			4 -20 43	RH	31/23	Paracentral lobule/cingulate gyrus	99	0.001
			-3 -48 23	LH	23	Posterior cingulate	439	< 0.001
			36 2 -38	RH	20	Middle and inferior temporal gyri	58	0.028
Controls – within	Increase	Increase	46 -45 43	RH	40	Inferior parietal lobule	3346	< 0.001

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	KE	Significance (p (corrected))
group			30 23 0	RH	43	Insula	339	< 0.001
			-35 21 1	LH	43	Insula	144	< 0.001
			42 44 18	RH	10/8	Middle frontal gyrus	212	< 0.001
			-27 1 55	LH	6	Middle frontal gyrus	2011	< 0.001
			0 -62 -18	LH/RH		Declive/culmen	250	< 0.001
			-25 -66 -18	LH		Declive/culmen	268	< 0.001
			-43 11 23	LH	46	Inferior frontal gyrus	164	< 0.001
			-35 61 6	LH	10	Middle frontal gyrus	77	0.014
			42 -58 -23	RH		Tuber/culmen	103	0.002
			46 -42 26	RH	40	Inferior parietal lobule/superior temporal gyrus	68	0.027
			12 -14 -15	RH		Thalamus	132	< 0.001
			20 54 -15	RH	6	Superior frontal gyrus	73	0.018
			-45 31 30	LH	9	Middle frontal gyrus	65	0.033
Controls – within group	Increase	Decrease	-1 -52 23	LH	23	Posterior cingulate	1624	< 0.001
			40 -7 -2	RH	43	Insula	1032	< 0.001
			4 51 14	LH/RH	9/6	Medial and superior frontal gyri	2695	< 0.001
			-25 -12 -20	LH	20	Parahippocampal and fusiform	221	< 0.001

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	KE	Significance (p (corrected))
						gyri	380	< 0.001
			0 -24 40	LH/RH	5	Paracentral lobule		
							202	< 0.001
			55 3 -24	RH	21	Middle temporal gyrus		
							122	0.001
			26 -38 -7	RH	20	Parahippocampal and fusiform gyri		
							108	0.002
			-25 -44 -9	LH	37	Parahippocampal gyrus		
							86	0.007
			-45 8 -28	LH	21	Middle temporal gyrus		
							132	< 0.001
			-27 -17 -10	LH	40	Superior temporal gyrus		
							181	< 0.001
			-49 -65 31	LH	39	Angular gyrus		
							149	< 0.001
			-5 9 -6	LH	25/24	Caudate and anterior cingulate		
							161	< 0.001
			-43 2 -34	LH	21	Middle temporal gyrus		
							59	*0.052
			50 -58 27	RH	41	Superior temporal gyrus		
							63	0.039
			-35 -20 8	LH	43	Insula		
Patients – within group	0 correct	Increase	-7 1 55	LH	6	Medial frontal gyrus	71	0.004
			-31 -15 60	LH	6	Precentral gyrus	57	0.023
			22 -52 -18	RH		Culmen	87	0.001
Patients – within group	0 correct	Decrease	-49 -36 -9	LH		Temporal lobe – sub-gyral	51	0.028
			-52 -53 3	LH	21	Middle temporal gyrus	73	0.003
Patients – within group	1 correct	Increase	-27 -16 1	LH		Putamen and globus pallidus	63	0.007
			-7 1 55	LH	6	Medial and superior frontal gyri	98	< 0.001

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	KE	Significance (p (corrected))
			-31 -17 62	LH	6	Precentral and middle frontal gyri	94	< 0.001
			26 -47 -22	RH		Culmen	101	< 0.001
Patients – within group	1 correct	Decrease	-52 -53 5	LH	21	Middle temporal gyrus	109	< 0.001
			14 -55 5	RH	30	Cuneus	83	0.001
			-7 -46 34	LH	31	Precuneus and cingulate gyrus	52	0.022
			42 -39 -12	RH	20	Fusiform gyrus	51	0.025
			14 -83 24	RH	30	Cuneus	54	0.018
Patients – within group	2 correct	Increase	22 -52 -18	RH		Culmen	59	0.012
			32 5 57	RH	9	Middle frontal gyrus	74	0.003
			-31 -17 60	LH	6	Precentral gyrus	57	0.015
Patients – within group	2 correct	Decrease	-11 -36 37	LH	31	Cingulate gyrus	266	< 0.001
			-5 -77 0	LH	18	Lingual gyrus	62	0.009
			-46 -36 -9	LH		Temporal lobe – sub gyral	71	0.004
			-9 -57 12	LH	23/30	Posterior cingulate	110	< 0.001
			14 -83 24	RH	18	Cuneus	157	< 0.001
			-52 -53 5	LH	21	Middle temporal gyrus	150	< 0.001
			-50 -23 -13	LH	21	Middle temporal gyrus	61	0.010
			8 -52 19	RH	23	Posterior cingulate	49	0.033
			14 -51 1	RH	18/19	Lingual gyrus	81	0.002

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	KE	Significance (p (corrected))
			-29 -34 -1	LH	37	Parahippocampal gyrus	52	0.024
			0 48 -6	LH	24/11	Anterior cingulate and medial frontal gyrus	66	0.006
			-13 -91 21	LH	30	Cuneus	45	0.050
Patients – within group	3 correct	Increase	-27 -16 3	LH		Putamen	197	< 0.001
			-37 -38 41	LH	6	Inferior parietal lobule and precentral gyrus	404	< 0.001
			22 -52 -18	RH		Culmen	136	< 0.001
			32 1 57	RH	6	Middle frontal and precentral gyri	204	< 0.001
			6 5 55	RH	6	Superior and medial frontal gyri	168	< 0.001
			-39 -70 -22	LH		Declive	59	0.007
			-21 -53 47	LH	7	Precuneus and superior parietal lobule	52	0.016
			38 18 1	RH	43	Insula	86	0.001
Patients – within group	3 correct	Decrease	-5 -77 0	LH	18	Lingual gyrus	94	< 0.001
			-13 -46 28	LH	7	Cingulate gyrus and precuneus	251	< 0.001
			-25 -32 -2	LH		Temporal lobe – sub-gyral	106	< 0.001
			10 -37 26	RH	31	Cingulate gyrus	48	0.024
			14 -51 1	RH	18	Lingual gyrus	757	< 0.001
			-47 -38 -4	LH	21	Middle temporal gyrus	241	< 0.001
			-3 51 12	LH/RH	10	Medial frontal gyrus	69	0.003

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			22 -82 -20	RH		Declive/Tuber	61	0.006
			0 -36 42	LH/RH	5	Paracentral gyrus	242	< 0.001
			-43 -62 27	LH	39	Middle temporal gyrus	84	0.001
			0 33 6	LH/RH	32	Anterior cingulate	78	0.001
			-11 -93 21	LH	19	Cuneus	68	0.003
			-23 -74 18	LH	31	Precuneus	42	0.048
			36 -38 -5	RH		Temporal lobe – sub gyral	98	< 0.001
			16 -85 32	RH	18	Cuneus	135	< 0.001
			-52 -23 -13	LH	21	Middle and inferior temporal gyri	44	0.038
			-60 -53 6	LH	21	Middle temporal gyrus	46	0.031
	Increase	Increase	34 21 0	RH	43	Insula	124	< 0.001
			26 5 57	RH		Frontal lobe – sub gyral	368	< 0.001
			36 -71 29	RH	19	Middle temporal gyrus and precuneus	436	< 0.001
			-43 6 35	LH	9/6	Precentral and middle frontal gyri	366	< 0.001
			-47 -43 56	LH	40	Inferior parietal lobule	861	< 0.001
			40 43 11	RH	6	Middle frontal gyrus	255	< 0.001
			-29 -68 -17	LH		Declive/tuber	228	< 0.001

Group comparison	Contrast	Activation effect	Cluster co-ordinates (x y z)	Hemisphere	BA	Location description	KE	Significance (p (corrected))
			55 -40 37	RH	40	Supramarginal gyrus and inferior parietal lobule	239	< 0.001
			-3 -59 53	LH	7	Precuneus and postcentral gyrus	192	< 0.001
			4 16 45	RH	6/8	Medial frontal gyrus	293	< 0.001
Patients – within group	Increase	Decrease	8 57 16	RH	10	Medial frontal gyrus	1336	< 0.001
			59 -9 -14	RH	21	Middle temporal gyrus	145	< 0.001
			-3 -36 46	LH	7/6/5	Precuneus, medial frontal gyrus, and paracentral lobule	2514	< 0.001
			-47 -69 35	LH	39	Angular gyrus and middle temporal gyrus	99	0.003
			61 -4 26	RH	6	Precentral gyrus	70	0.021
			-11 32 52	LH	8	Superior frontal gyrus	451	< 0.001
			-15 9 -13	LH	25/44	Inferior frontal and subcallosal gyri	63	0.036
			-15 -61 -4	LH	19	Lingual gyrus	83	0.008
			-39 -7 -2	LH	21	Middle temporal gyrus	196	< 0.001
			14 -48 0	RH	19	Lingual gyrus	66	0.029
			53 -38 2	RH	21	Middle temporal gyrus	59	0.049
			10 -60 20	RH	19	Precuneus and cuneus	159	< 0.001
			22 -84 -23	RH		Uvula	74	0.016
			-27 -39 -16	LH		Culmen	201	< 0.001
			40 –22 5	RH	43	Insula and precentral gyrus	322	< 0.001

Appendix 3C: Experiment Three: Significant fixed effects activations

Contrast: Session	Activation effect	Cluster Co-ordinates (x y z)	Hemisphere	Regions (BA)	Location description	K_E	Significance ($p_{(corrected)}$)
Increase: Both	Medication free > post-medication	38 -67 48 -19 41 2	RH LH	 24	Sub-gyral, white matter Anterior cingulate/medial frontal gyrus	969 280	< 0.001 0.008
Increase: First	Medication free > post-medication	34 -58 32 -7 -73 44	RH LH/RH	 7	Sub-gyral, white matter Precuneus	700 407	< 0.001 0.001
Increase: Second	Medication free > post-medication	-21 41 0	LH	11	Middle frontal gyrus	232	0.020
Decrease: Both	Medication free < post-medication	51 5 -6 -45 -73 6 10 -69 -9	RH LH RH	42 19	Superior temporal gyrus Middle occipital gyrus Cerebellum: culmen & declive	442 195 212	0.001 0.040 0.029
Decrease: First	Medication free < post-medication	-49 18 –20 57 -1 -1 -3 -39 61	LH RH LH	38 & 21 42 5	Superior and inferior temporal gyri Superior temporal gyrus Paracentral lobule and precuneus	1110 180 198	< 0.001 0.053* 0.037

Appendix 3D: Experiment Three: Significant random effects activations

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
Medication free – within group	0 vs. 1	0 < 1	2 -8 58	LH/RH	6	Medial frontal gyrus	686	< 0.001
			26 0 53	RH	6	Frontal lobe – sub-gyral	200	0.001
			44 -49 52	RH	40	Inferior parietal lobule	257	< 0.001
			-43 -37 53	LH	40	Inferior parietal lobule and pre- and post-central gyri	620	< 0.001
Medication free – within group	0 vs. 2	0 > 2	18 -91 16	LH/RH	18	Middle occipital gyrus	441	< 0.001
			24 -59 5	RH	18	Lingual gyrus	264	0.002
			-9 -59 1	LH	19	Lingual gyrus	125	*0.058
Medication free – within group	0 vs. 2	0 < 2	24 1 52	RH	6	Middle frontal gyrus	435	< 0.001
			36 -55 45	RH	40	Inferior parietal lobule	1023	< 0.001
			-25 -48 39	LH	40	Inferior parietal lobule	425	< 0.001
			8 16 43	LH/RH	6	Medial frontal gyrus	180	0.013
Medication free – within group	0 vs. 3	0 > 3	8 59 23	LH/RH	9/10	Superior and medial frontal gyrus	1148	< 0.001
			18 -62 -6	RH	18	Lingual gyrus	135	0.006
			-19 32 50	LH	8	Superior frontal gyrus	171	0.001
			-3 -38 35	LH	31	Cingulate gyrus and precuneus	290	< 0.001
			18 -89 25	LH/RH	18/19	Cuneus	202	< 0.001
			-1 -20 38	LH	31	Cingulate gyrus	146	0.004

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			-49 -66 27	LH	21	Middle temporal gyrus	155	0.003
			-29 -21 -11	LH	35	Parahippocampal gyrus	114	0.014
Medication free – within group	0 vs. 3	0 < 3	2 8 53	LH/RH	6	Superior and middle frontal gyri	3077	< 0.001
			51 9 20	RH	9	Inferior frontal gyrus	199	< 0.001
			42 49 14	RH	46/10	Middle frontal gyrus	938	< 0.001
			-29 -56 58	LH	7	Superior parietal lobule	4663	< 0.001
			40 18 5	RH	43	Insula	349	< 0.001
			8 -27 -14	LH/RH		Midbrain	144	0.004
			10 -56 -11	RH		Declive/culmen	599	< 0.001
			-33 -68 -24	LH		Uvula/culmen	116	0.013
			-9 -17 -1	LH		Globus pallidus	114	0.014
			-35 18 1	LH	43	Insula	198	< 0.001
			16 10 0	RH		Putamen and globus pallidus	185	0.001
			18 -14 14	RH		Ventral lateral nucleus	234	< 0.001
Medication free – within group	1 vs. 2	1 > 2	12 -63 5	RH	18	Lingual gyrus	724	< 0.001
			-23 -50 -2	LH	18/37	Lingual and parahippocampal gyri	1010	< 0.001
			0 -86 6	LH/RH	18	Cuneus	209	< 0.001
			55 -25 20	RH	40	Postcentral gyrus	206	< 0.001

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			46 -15 1	RH	41	Superior temporal gyrus	285	< 0.001
			-15 50 32	LH	9	Superior frontal gyrus	87	0.033
Medication free – within group	1 vs. 2	1 < 2	28 1 50	RH	6	Middle frontal gyrus	280	< 0.001
			46 -38 42	RH	40	Inferior parietal lobule	112	0.010
			30 -55 38	RH	7	Superior parietal lobule and precuneus	325	< 0.001
Medication free – within group	1 vs. 3	1 > 3	-60 -33 18	LH	42	Superior temporal gyrus	209	< 0.001
			-19 -23 -15	LH	30	Parahippocampal gyrus and posterior cingulate	926	< 0.001
			10 -56 -3	RH	18	Lingual gyrus	434	< 0.001
			4 -18 43	LH/RH	31	Cingulate gyrus	822	< 0.001
			8 63 19	LH/RH	10/6	Superior frontal gyrus	1196	< 0.001
			-47 -64 27	LH	21	Middle temporal and angular gyri	195	0.001
			-5 -79 22	LH	18	Cuneus	208	< 0.001
			32 -29 -13	RH	35	Parahippocampal gyrus	218	< 0.001
			50 -11 1	RH	22/38	Superior and middle temporal gyri	956	< 0.001
			26 -29 66	RH	3	Postcentral gyrus	124	0.011
			-50 -13 0	LH	22/38	Superior and middle temporal gyri	302	< 0.001
			-9 -96 9	LH	18	Cuneus	87	*0.054

C

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			-1 -36 33	LH	31	Cingulate gyrus	137	0.006
			2 50 -13	LH/RH	32	Anterior cingulate and middle frontal gyrus	113	0.017
Medication free – within group	1 vs. 3	1 < 3	38 42 26	RH	10/9	Middle and superior frontal gyri	251	< 0.001
			22 -70 57	RH	7	Precuneus	594	< 0.001
			26 5 53	RH	6	Middle frontal gyrus	390	< 0.001
			2 12 55	LH/RH	6/8	Superior and medial frontal gyri	174	0.002
			46 –41 50	RH	40	Inferior parietal lobule	105	0.024
Medication free – within group	Increase	Increase	24 2 50	RH	6	Middle frontal gyrus	728	< 0.001
			44 49 14	RH	46	Middle and superior frontal gyri	583	< 0.001
			0 3 55	LH/RH	8	Superior frontal gyrus	622	< 0.001
			-17 -66 57	LH	7/40	Superior and inferior parietal lobule	3064	< 0.001
			-25 -6 50	LH	6	Middle frontal gyrus	118	0.013
			28 -61 -28	RH		Pyramis	189	0.001
Medication free – within group	Increase	Decrease	18 -62 -6	LH/RH	18	Lingual gyrus	2835	< 0.001
			18 -93 16	LH/RH	18	Middle occipital gyrus and cuneus	859	< 0.001
			40 -19 -1	RH	35/38	Parahippocampal and superior temporal gyri	1057	< 0.001
			-49 -65 36	LH	39/21	Angular and middle temporal gyri	206	< 0.001
			-45 25 -10	LH	11	Middle and inferior frontal gyri	92	0.040

CI

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			26 -27 60	RH	4	Precentral and postcentral gyri	142	0.005
			-37 -20 -1	LH	22/21	Claustrum and superior temporal gyrus	498	< 0.001
			-1 49 14	LH/RH	6	Medial frontal gyrus	910	< 0.001
			-17 48 34	LH	8	Superior frontal gyrus	478	< 0.001
			-13 63 12	LH	8	Superior frontal gyrus	102	0.026
			2 -48 -3	RH		Culmen	122	0.011
Post-medication – within group	0 vs. 2	0 > 2	-19 28 54	LH	6	Superior frontal gyrus	144	0.013
Post-medication – within group	0 vs. 2	0 < 2	53 -41 50	RH	40/7/39	Inferior parietal lobule and angular gyrus	750	< 0.001
			28 11 60	RH	6	Middle frontal gyrus	226	0.001
			-25 -48 39	LH	40	Inferior parietal lobule	236	0.001
			40 31 37	RH	9	Middle and superior frontal gyri	124	0.027
Post-medication – within group	0 vs. 3	0 > 3	-50 -64 27	LH	39	Middle temporal and angular gyri	188	< 0.001
			0 63 10	LH/RH	32	Anterior cingulate and medial frontal gyrus	311	< 0.001
			-5 -56 -25	LH	31	Posterior cingulate	719	< 0.001
			-11 52 38	LH	9/10	Medial and superior frontal gyri	197	< 0.001
			14 -79 22	RH	18	Cuneus	115	0.002
			-1 -15 38	LH/RH	31		196	< 0.001

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance (p (corrected))
						Cingulate gyrus		
			-7 35 46	LH	6		202	< 0.001
						Superior frontal gyrus		
			8 54 23	LH/RH	9		76	0.019
						Superior frontal gyrus		
			-33 -15 -12	LH	35		67	0.034
						Parahippocampal gyrus		
Post-medication – within group	0 vs. 3	0 < 3	8 -70 51	LH/RH	7	Precuneus and superior parietal lobule	6939	< 0.001
			40 35 35	RH	9/10		755	< 0.001
						Middle and superior frontal gyrus		
			28 1 55	RH	6		1000	< 0.001
						Middle frontal gyrus		
			51 11 16	RH	45		66	0.037
						Inferior frontal gyrus		
			-31 18 1	LH	43		346	< 0.001
						Insula		
			38 18 3	RH	43/47/45		309	< 0.001
						Insula and inferior frontal gyrus		
			20 -8 15	RH			140	< 0.001
						Putamen		
			-33 30 26	LH	9	Middle frontal gyrus	189	< 0.001
			6 -60 -14	RH		Declive/culmen	286	< 0.001
			-31 -51 -28	LH		Declive	197	< 0.001
			32 -47 -30	RH		Culmen	65	0.039
Post-medication – within group	1 vs. 2	1 > 2	-52 -62 23	LH	39	Middle temporal and angular gyri	160	0.005
			0 -44 26	LH/RH	23	Posterior cingulate	680	< 0.001
			8 -75 28	LH/RH	18	Cuneus	186	0.002

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			18 35 44	RH	8	Superior frontal gyrus	126	0.016
			-15 46 36	LH	8	Superior frontal gyrus	334	< 0.001
			-47 -5 -4	LH	22	Superior temporal gyrus	142	0.009
			-3 -3 35	LH/RH	24	Cingulate gyrus	301	< 0.001
			-1 50 20	LH/RH	9	Medial frontal gyrus	234	< 0.001
Post-medication – within group	1 vs. 3	1 > 3	0 -14 45	LH	24	Cingulate gyrus	1288	< 0.001
			0 57 12	LH/RH	10/8	Middle and superior frontal gyri	1110	< 0.001
			-25 -25 -13	LH	35	Parahippocampal gyrus	167	< 0.001
			-47 -62 27	LH	39	Middle temporal and angular gyri, and precuneus	168	< 0.001
			40 -9 -7	RH	22	Superior temporal gyrus	106	0.002
			-35 -18 16	LH	43	Insula	59	0.042
			-3 21 62	LH	6	Superior frontal gyrus	78	0.010
			22 36 52	RH	8	Superior frontal gyrus	66	0.025
Post-medication – within group	1 vs. 3	1 < 3	12 -53 49	LH/RH	7	Precuneus and superior parietal lobule	1152	< 0.001
			-31 25 1	LH	43	Insula	108	0.001
			32 5 57	RH	6	Middle frontal gyrus	232	< 0.001
			36 23 0	RH	45/47	Inferior frontal gyrus	90	0.005
			-27 -66 -23	LH		Uvula/culmen	93	0.004

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			46 -42 41	RH	40/7	Inferior parietal lobule	304	< 0.001
			-27 -47 41	LH	40	Supramarginal gyrus	64	0.029
			-27 0 63	LH	6	Superior and middle frontal gyrus	62	0.033
Post-medication – within group	2 vs. 3	2 < 3	-27 -87 21	LH	18	Middle occipital gyrus	90	*0.055
			0 -66 53	LH/RH	7	Superior parietal lobule and precuneus	936	< 0.001
			2 18 41	RH	6	Superior frontal and cingulate gyri	129	0.011
			-39 47 16	LH	10	Middle frontal gyrus	137	0.008
Post-medication – within group	Increase	Increase	-31 18 3	LH	43	Insula	256	< 0.001
			32 7 59	RH	6	Middle frontal gyrus	556	< 0.001
			-45 -37 50	LH	7	Inferior and superior parietal lobules and precuneus	3767	< 0.001
			38 48 22	LH/RH	10	Superior and middle frontal gyri	333	< 0.001
			51 11 18	RH	9	Inferior frontal gyrus	62	*0.054
			36 20 3	RH	43/47	Insula and inferior frontal gyrus	205	< 0.001
			4 11 55	LH/RH	6	Superior and middle frontal gyri	844	< 0.001
Post-medication – within group	Increase	Decrease	-1 -15 36	LH/RH	24/31	Cingulate gyrus	2016	< 0.001
			-50 -64 25	LH	39	Middle temporal and angular gyri	242	< 0.001
			-17 30 48	LH/RH	8	Superior frontal gyrus	1779	< 0.001
			10 -77 32	LH/RH	18/19	Cuneus	233	< 0.001
			14 -16 41	RH	24	Cingulate gyrus	102	0.004

Group Comparison	Contrast	Activation Effect	Cluster Co-ordinates (x y z)	Hemisphere	BA	Location description	K_E	Significance ($p_{(corrected)}$)
			-29 -19 -13	LH		Hippocampus	172	< 0.001
			-9 -71 4	LH	18	Lingual gyrus	64	0.048